An Ireland-Claisen approach to beta-hydroxy alpha-amino acids

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AN IRELAND-CLAISEN APPROACH TO β-HYDROXY α-AMINO ACIDS

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Abstract

In 1991, Ireland reported the rearrangement of an allylic ester containing an allylic enol ether.[1] This was followed by the publication of Kazmaier who reported the chelated enolate rearrangement of allylic amino esters.[2] It was envisaged that the combination of these two fragments would lead to a suitable allylic enol ether amino ester substrate that upon rearrangement would deliver β-hydroxy α-amino acids.

Initial efforts investigated the synthesis of the desired allylic enol ether amino esters with several routes being pursued. After significant investigation, synthesis of an allylic amino ester substrate was successfully completed. With the required substrate in hand significant investigation into employing Kazmaiers' protocol was found to be detrimental to the desired rearrangement, instead promoting competitive decomposition pathways. Switching to imide nitrogen protection and employing a more traditional Ireland-Claisen protocol, the allylic amino ester underwent a *syn*-selective [3,3]-sigmatropic rearrangement. This rearrangement was seen to be general, with a large range of *O*-functionality being investigated and offering yields of 50 – 81% and diastereoselectivites of ≥8:1.

The rearrangement of several other allylic amino esters, containing other protecting groups lead to little or no selectivity being observed, however utilizing *N*-diboc glycine the rearrangent was observed to take place with diastereoselective control. A study of the formation of the silyl ketene acetals showed a correlation between the (*E*)/(*Z*) geometry of the silyl ketene acetal formed and the diastereoselectivity observed within the rearrangement of the methoxy enol ether derived allylic amino ether substrate. The rearrangement using *N*-diboc glycine based substrates was also seen to be general with a range of *O*-functionality offering yields of 40 – 80% all being obtained as single diastereomers.

Access to the *anti*-diastereomer has been limited, being achieved in a 58% yield with a diastereoselectivity of 1.5:1. Several other transformations of the β-alkoxy α-amino esters products have also been shown. Finally the developed methodology was incorporated in a formal synthesis of furanomycin starting from (*S*)-butyn-2-ol, in 4.9% in 8 steps.

Contents

Acknowledgements

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Secondly, thanks go out to Dr. Barrie Marsh, for the constant support and advice. Baz without you the lab would not have been the same, although I'm certain have not listened to Lionel since the day you left! And yes, I have learnt you can not just use "The force" to hold a distillation together. Thanks for all the help, it's been extremely appreciated!

To everyone else, past and present members of the Carbery group, Andy, Wez, Steve, Nath, Matt and Moe, thanks for making our lab an absolutely fantastic working atmosphere! Without you bunch of alpha males (I think that's one of the many names we've been given), the past few years would have been really, really dull! You've all contributed in so many different ways, too many to go into.

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And finally, Tracy, ever since I have known you, you have given constant support, company and so much fun along the way. I hope you know that through your constant support you have helped me so much to be in this position I am today. For this I thank you so much!

Abbreviations

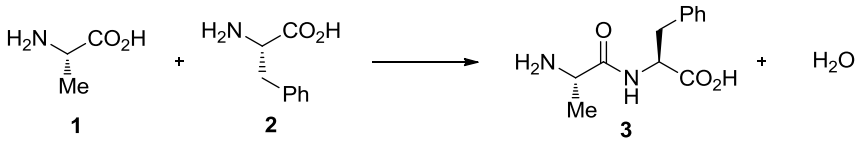
Ac	acetyl
app d	apparent doublet
app t	apparent triplet
aq	aqueous
AQN	anthraquinone
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binapthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
BTTP	*tert*-butyliminotri(pyrrolidino)-phosphorane
Bz	benzoyl
Cat	catalyst
Cbz	benzyloxycarbonyl
cf.	*confer*
CMC	*N*-cyclohexyl-*N'*-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DET	diethyl tartrate
DHQD	dihydroquinidine
DIBAL-H	diisobutyl aluminium hydride
DMAP	4-dimethylamino pyridine
DMF	dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
$_{D}$TA	D-threonine aldolase
DTT	dithiothretiol
E	electrophile
EDCi.HCl	1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
Equiv	equivalents
Et	ethyl
Grubbs (I)	benzylidene-*bis*(tricyclohexylphosphine)dichlororuthenium
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
hr	hour(s)
Hz	hertz
^{i}Pr	isopropyl

KHMDS	potassium hexamethyldisilizide
LiICA	lithium dicyclohexylamine
LiHMDS	lithium hexamethyldisilizide
LDA	lithium diisopropylamine
$_{L}$TA	L-threonine aldolase
m	multiplet
Me	methyl
MOM	methoxymethyl ether
MPLC	medium pressure liquid chromatography
MX_n	metal
m/*z*	mass charge ratio
NaHMDS	sodium hexamethyldisilizide
NBS	*N*-bromosuccinimde
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NOe	nuclear overhauser effect
P	protecting group
Ph	phenyl
PHAL	phthalazine
PhH	benzene
PhMe	toluene
Phth	phthaloyl
PLP	pyridoxal phosphate
PMB	*p*-methoxybenyzl
PMP	*p*-methoxyphenol
Pybox	2,6-*bis*[(4*R*)-4-phenyl-2-oxazolinyl]pyridine
q	quartet
quin	quintet
qt	quintet of triplets
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
RT	room temperature
s	singlet
SHMT	serine hydroxyl-methyl transferase
sept	septet
SKA	silyl ketene acetal
t	triplet
TBS	*tert*-butyldimethylsilyl
TEMP	2,2,6,6-tetramethylpiperidine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride

CHAPTER 1 INTRODUCTION

1.1 PEPTIDES

Peptides are natural polymers consisting of a series of up to fifty amino acid monomers, linked *via* a peptide bond under nucleic control.[3] Synthetic preparation either *in vivo* or *in vitro*, usually takes place *via* condensation reactions, however activation of the reaction differs (Scheme 1).



Scheme 1: Peptide bond formation

The structure of the peptides can be further elaborated by *inter*- and/or *intra*-chain interactions of side chains and therefore lead to a tertiary structure. With human biochemistry being regulated by peptic hormones and enzymatic pathways, it critical for stereochemical information contained upon the amino acids fragments to be retained during peptide synthesis.[3] Vasopressin **4**, a pituitary nonapeptide, was one of the first peptides to be prepared synthetically and displays an *intra*-molecular interaction with a disulfide bond formed between the two cysteine moieties (Figure 1).[3]

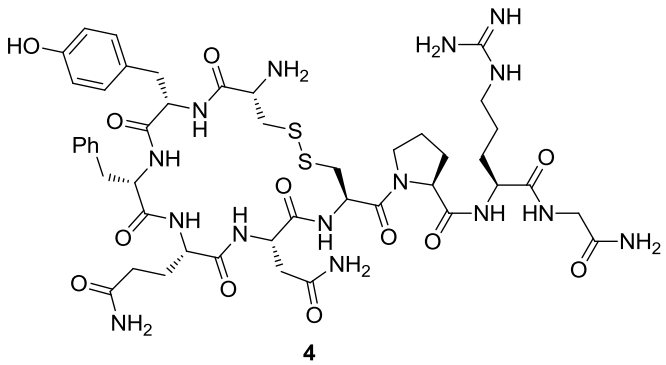


Figure 1: Vasopressin

Due to the overall complexity of peptides and proteins, a trivial system of naming has been developed. Each proteinogenic amino acid has been assigned a three letter code (Appendix 7.1). Using this system, individual amino acids along the protein chain can

easily be identified. Vasopressin **4** has again been represented below, using the abbreviated formula (Figure 2).

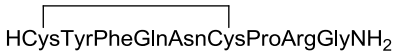


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Figure 2: Abbreviated representation of Vasopressin

1.1.1 *Amino acids*

Amino acids are molecules that contain both carboxylic acid and amine functionalities. Proteinogenic amino acids are the twenty naturally occurring amino acids that are found within proteins and that are coded for in the standard genetic code.[4] Proteinogenic literally means 'protein-building' and it is these amino acids that make up the peptides and proteins that are crucial to life.[4-5]

Nomenclature of amino acids

The most common type of amino acids found in nature are α-amino acids. These amino acids comprise of both the carboxylic acid and amine functionalities bonded to the same α-carbon. Other types of amino acids are classified by the number of carbon linkers separating the amine and carboxylic acid functional groups, as demonstarted below with alanine (Figure 3).

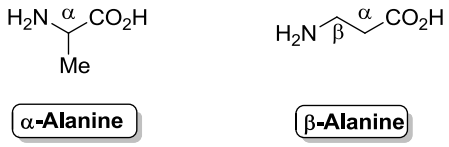

Figure 3: Examples of α- and β-amino acids

Another type of nomenclature refers to the specific enantiomer of an amino acid. The L- and D- nomenclature does not refer to the optical activity of the amino acid, instead this refers to the optical activity of the isomer of glyceraldehyde that the amino acid can theoretically be synthesized from (Figure 4).[6] Alternatively, (*R*) or (*S*) designators can be used to indicate absolute stereochemistry of the specific amino acid.

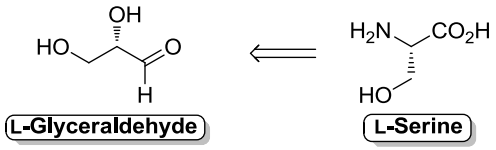

Figure 4: Theoretical synthesis of L-serine

1.1.2 *β-Hydroxy α-amino acids*

β-Hydroxy α-amino acids are seen as an important subgroup of amino acids. The importance of these molecules can be displayed with two key examples that represent 10% of proteinogenic amino acids: threonine and serine.

Threonine

Threonine is one of the eight essential amino acids, so called, since they must be obtained from food or other sources, since synthesis cannot occur within the body.[7] The threonine moiety is susceptible to many post-translational modifications. The hydroxyl group can undergo *O*-linked glycosylation and also phosphorylation can occur through the action of threonine kinase.

With two chiral centres, four possible stereoisomers of threonine can exist. L-threonine refers to one diastereomer whereas L-*allo*-threonine refers to the other. The same is applicable to D-threonine (Figure 5).

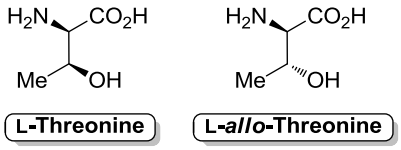

Figure 5: Diastereomers of L-threonine

Serine

Serine is not considered an essential amino acid. In healthy adults, serine can be synthesized within the body *via* a condensation between glycine and activated formaldehyde. However, in clinical situations such as impaired kidney function, endogenous synthesis may not cover serine requirements and therefore supplements maybe required. Therefore, serine becomes an essential amino acid for patients with poor kidney functions.[8]

1.2 β-HYDROXY α-AMINO ACIDS IN NATRUAL PRODUCTS

The β-hydroxy α-amino acid moiety is prevalently distributed throughout a significant number of compounds isolated from natural products, with a sizeable proportion having biological activity.[9] None of the examples detailed below include serine or threonine containing peptides and in all examples the β-hydroxy α-amino acid functionality highlighted in red.

1.2.1 *β-Hydroxy α-amino acids*

The β-hydroxy α-amino acid moiety is found in large number natural products. For example, kaitocephalin **7** (Figure 6), was first isolated in 1997 by Shin-Ya and co-workers from the filamentous fungus *Eupenicillium shearii* PF1191.[10] This novel pyrrolidine based alkaloid is a naturally occurring glutamate receptor antagonist. Initial biological screening showed a suppression of kainic acid toxicity with an EC_{50} value of 0.68 μM concentration. These results prompted kaitocephalin to be examined as a potential lead compound in the development of therapeutic agents to treat neurological diseases caused by glutamate excitotoxicity.[11]

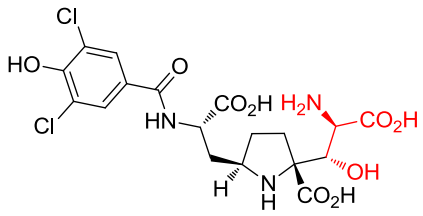

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Figure 6: Kaitocephalin

Sphingofungins were first isolated from *Aspergillus* and *Paeciomyces* in 1982 within the laboratories at Merck.[12] This class of compounds has significant antifungal properties, acting as inhibitors of serine palmitoyl transferease.[13] These novel polyhydroxyamino acids, containing four contiguous stereocentres makes these compounds particularly interesting as total synthesis targets. Sphingofungin E, **8** (Figure 7), has attracted the most recent interest, due to potent immunosuppressive activity.[14]

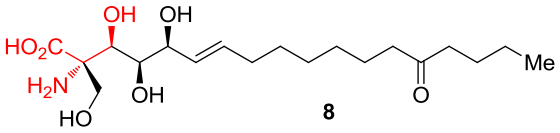

Figure 7: Sphingofungin E

Altemicidin **9** (Figure 8), a six-azainden monoterpene alkaloid was first isolated from the a group of gram-positive bacteria *Actinomycete*, in 1989 by Takeuchi and co-workers.[15] Strong acaricidal activity along with the inhibition of tumour cell growth shows the importance of this compound.

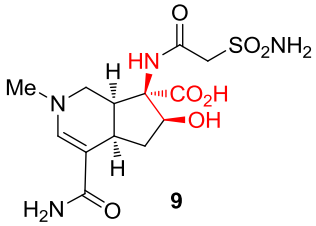

Figure 8: Altemicidin

1.2.2 *β-Alkoxy α-amino acids*

Several natural products contain alkylated β-hydroxy α-amino acids. Brasilicardin A **10** (Figure 9), was first isolated from the cultured broth of *Nocardia brasiliensis* IFM0406 by Kobayashi *et al.* in 1998.[16] This compound consists of a β-alkoxy α-amino acid and a sugar moiety based upon a perhydrophenanthrene skeleton. Preliminary investigations showed strong immunosuppressive activity in a mouse mixed-lymphocyte reaction assay system with an IC_{50} value of 0.057 μg/mL.[17] Brasilicardin A also exhibits strong antifungal activity against several other screens. When tested against 38 human tumour cell lines, brasilicardin A showed a striking pattern of differential cytotoxicity, however no significant correlations against known antitumor compounds were observed.

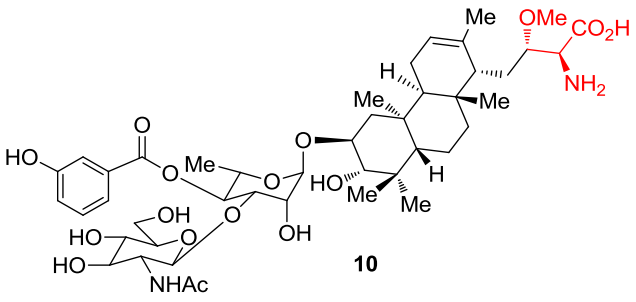

Figure 9: Brasilicardin A

Renieramycin D **11** (Figure 10), is a member of a growing family of antimicrobaial metabolites isolated from a bright blue sponge of the genus *Reniera* in 1982 by Faulkner *et al.*[18] These isoquinolinequinone antibiotics have shown potential for antitumour activity.[19]

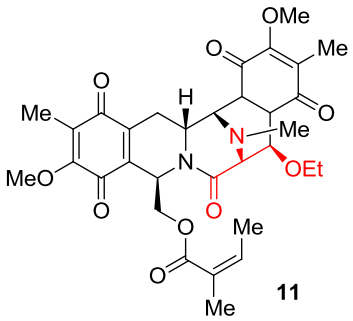

Figure 10: Renieramycin D

Pauamides A and B, two cyclic depsipeptides that have been isolted from a collection of marine sponges *Theneolla mirabilis* and *Theonella swinhoei* in 1999, by Andersen *et al.*[20] Structurally, pauamide A **12**, comprises of a 22-membered macrocycle connected to a complex linear tetrapeptide through an amide bond (Figure 11). Several non-proteinogenic amino acid residues are present and in particular several β-alkoxy α-amino acid subunits including β-methoxytyrosine.[21] Recent interest in these molecules is due to their strong inhibitory effect on the infection of human T-lymphoblastoid cells by HIV-1_{RF}, with an EC_{50} value of 4 ng/mL.

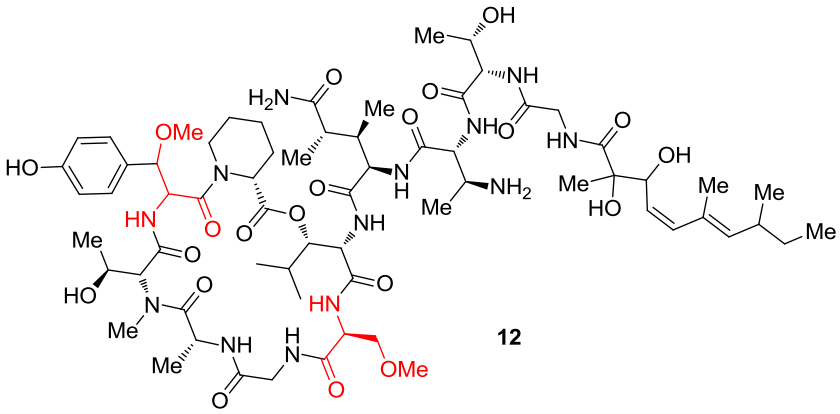

Figure 11: Pauamide A

Callipeltin A **13** (Figure 12), another cyclic depsipeptide was first isolated from a shallow water marine sponge of the genus *Callipelta* by Minale *et al.* in 1999.[22] More recently the group of Luciani has shown that it acts as a powerful inhibitor of cardiac

sodium/calcium exchanger and therefore would be extremely useful as a regulator of myocardial contractility.[23]

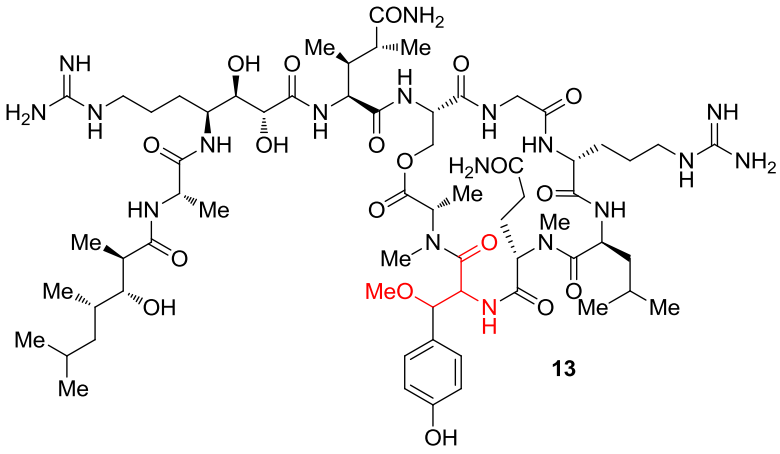

Figure 12: Callipeltin A

The family of cyclomarins were isolated from a marine bacterium in 1999 by Clardy *et al.*[24] The major constituent, cyclomarin A **14** (Figure 13), displays significant anti-cancer and anti-inflammatory activities both in, *in vitro* and *in vivo* assays. Intensive biological evaluation of cyclomarin C is somewhat limited due to the low availability of only 3% from nature.[25] These cyclic heptapeptides each contain four non-coded amino acids, including β-methoxyphenylalanine, another β-alkoxy α-amino acid subunit.

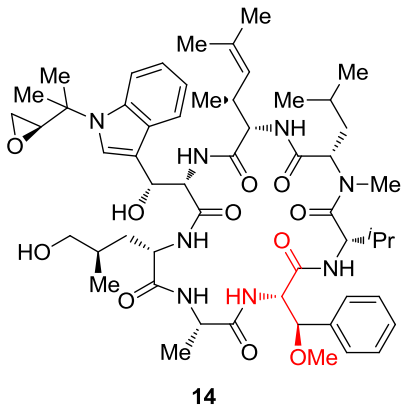

Figure 13: Cyclomarin A

1.2.3 *β-Aryloxy α-amino acids*

There are also several examples of β-aryloxy α-amino acids within nature, typically based around a similar cyclopetide alkaloid structure. Sanjoinine G1 **15** (Figure 14), is one cyclopeptide alkaloid that has been isolated from the seed of *Zizyphus vulgaris* var.

spinosus by Han *et al.* in 1989.[26] These seeds have reportedly been used in the treatment of insomnia in Chinese herbal medicine.[27]

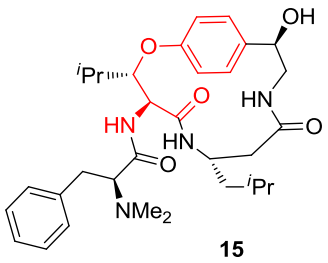

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Figure 14: Sanjoinine G1

Adouetine Y **16** (Figure 15), another cyclopeptide alkaloid which was isolated from *Melochia corchorifolia* by Tschesche and Reutel in 1968.[28] Extracts from this species of plant found in hot parts of India have been reported in folk law as medicines to cure dysentery and watersnake bites.[29]

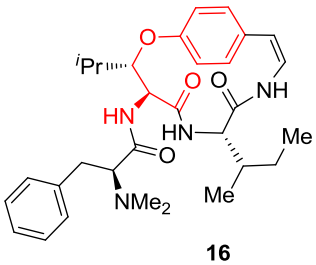

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Figure 15: Adouetine Y

1.2.4 *β-Cyclic ether α-amino acid derivatives*

Several examples of naturally occurring β-hydroxy α-amino acids have the β-hydroxy functionality contained within a five/six member ring. Polyoxins are a class of pyrimidine nucleoside peptide antibiotics isolated from *Streptomyces cacaoi* var. *asoensis* by Isono *et al.* in 1969.[30] Polyoxins have displayed noteworthy activity against phytopathogenic fungi whilst being ineffective against plants or animals, therefore making them ideal candidates for agricultural fungicides.[31]

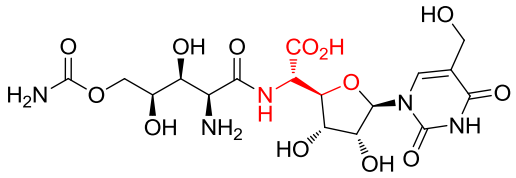

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Figure 16: Polyoxin B

Amipurimycin **18,** (Figure 17) is a complex member of a family of peptidyl nucleosides isolated from *Streptomyces novoguineensis sp.* by Kishi *et al*. in 1976.[32] Amipurimycin displays outstanding antifungal activity against several phytopathogenic fungi. In field tests, it showed exceptional control of blast disease of rice plants. However, only limited toxicity studies have been carried out.

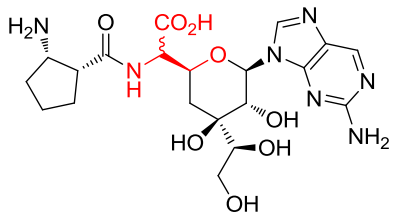

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Figure 17: Amipurimycin

Miharamycins A and B (Figure 18) were both isolated from *Streptomyces miharaensis* SF-489 by Niida *et al.* in 1967.[33] The peptidyl nucleosides have also been to have strong inhibitory activity against the rice blast disease caused by *Pyricularia oryzae*.[33]

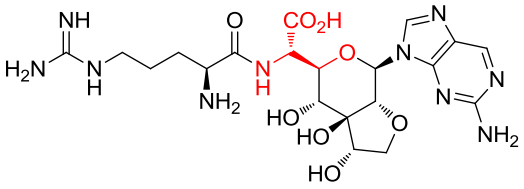

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Figure 18: Miharamycin B

1.2.5 *β-Hydroxy α-amino acid acyl derivatives*

Several β-hydroxy α-amino acid acyl moieties are present in a large number of biologically active molecules. Salinosporamide A **20** (Figure 19), a densely functionalized γ-lactam-β-lactone bicycle, was isolated by Feical and co-workers in

2003 as a bioactive product of a marine actinomyctete bacterium commonly found within ocean sediment.[34] Biological testing of salinosporamide A showed it to be an extremely effective proteasome inhibitor, displaying high *in vitro* cytotoxic activity against several tumour cells lines with IC_{50} values of less then 10 nM.[35] Such is the activity, this potential anticancer agent recently entered phase I of human clinical trials for the treatment of multiple myeloma.[36]

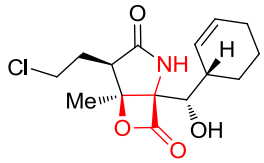

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Figure 19: Salinosporamide A

Oxazolomycin A **21** (Figure 20), was isolated from the fermented broth of *Streptomyces sp*. in 1985 by Uemura *et al.* during their study into molecules with inhibitory activity against Ehrlich ascites tumour.[37] Oxazoloymcins exhibit a wide range of antibitotic activity against gram-positive bacteria, antiviral activity against vaccinia, herpes simplex type I and influenza A, as well as *in vivo* anti-tumour activity.[38]

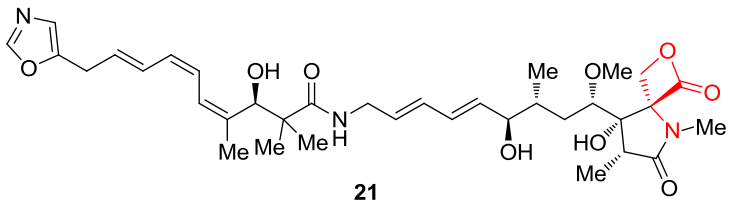

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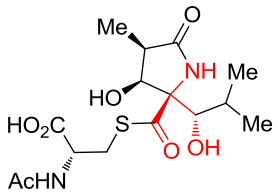
Figure 20: Oxazolomycin A

Lactacystin **22** (Figure 21), a γ-lactam, was isolated from a cultured broth of *Streptomyces sp.* OM-6519 by Omura *et al*. in 1991.[39] This compound induces neurite outgrowth in the neuroblastoma cell line therefore prompting a study in the use against neurologically related diseases such as Alzheimer's.[40]



22

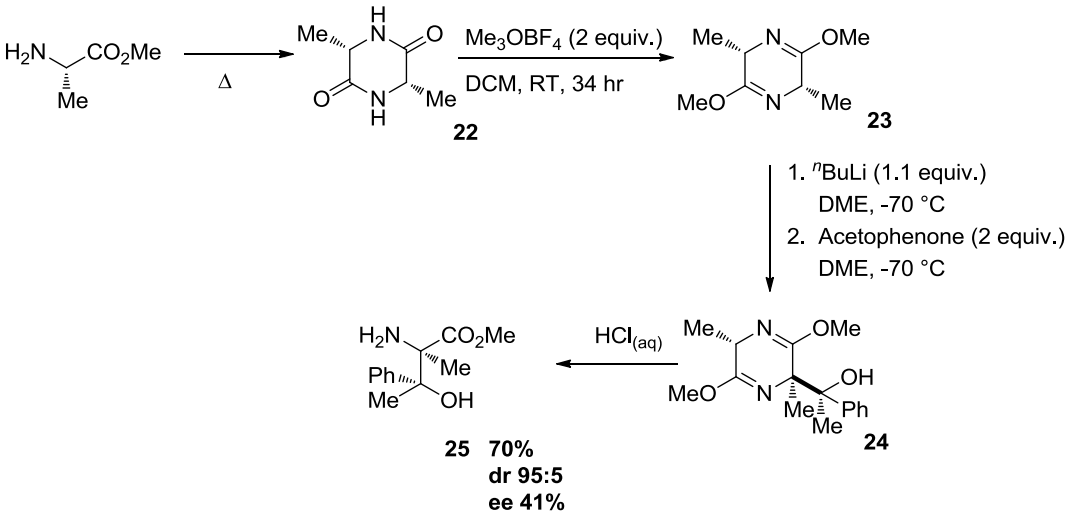
Figure 21: Lactacystin

1.3 SYNTHESIS OF β-HYDROXY α-AMINO ACIDS

Due to the importance of the β-hydroxy α-amino acid moiety and the large proportion of β-hydroxy α-amino acid containing natural products, there has been significant interest within the synthetic organic community towards the preparation of these compounds. As such, in recent years a significant number of protocols have been developed and existing methods have been improved, thus showing the importance of this class of compound. One of the major challenges of synthesizing the β-hydroxy-α-amino acid unit is obtaining control of diastereo- and enantioselectivity. As a result, complete control in the synthesis of β-hydroxy-α-amino acids presents a challenging and desirable target to synthetic chemists. Several routes towards these compounds will now be discussed:

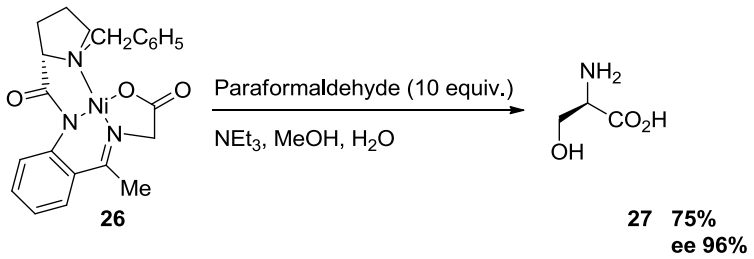
1.3.1 *Aldol reactions*

The first example of the use of an aldol condensation in the synthesis of β-hydroxy α-amino acids was reported by Schöllkopf *et al*. in 1980 (Scheme 2).[41] Starting from L-alanine methyl ester and subjecting this to heat, afforded cyclic dimer **23**. Reacting dimer **23** with trimethyloxonium tetrafluoroborate delivered the required bis-lactim **24**. The ensuing aldol condensation between **24** and acetophenone, followed by acidic work-up generated the β-hydroxy-α-amino ester **25** in good yield and high diastereoselectivity with a moderate enantiomeric excess. Remaining L-alanine methyl ester starting material could also be recovered.



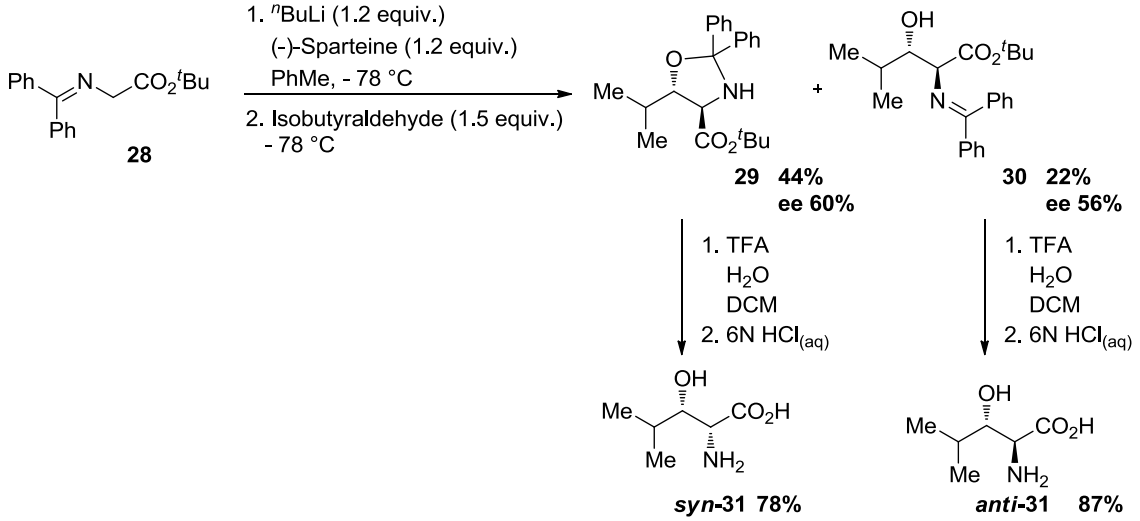
Scheme 2: Synthesis of the β-hydroxy α-amino acid moiety *via* an aldol condensation of L-alanine methyl ester

Belokon *et al.* reported the condensation of formaldehyde with a Nickel (II) schiff base and chiral glycine derivative complex **26**, to afford (*S*)-serine **27** in high enantiomeric excess in 1985 (Scheme 3).[42] A switch in reactivity was observed to afford (*R*)-serine should the reaction be carried out in the of presence sodium methoxide at a concentration of greater than 0.2 N, however a reduced enantiomeric excess is obtained.



Scheme 3: Aldol condensation utilizing a nickel schiff base complex

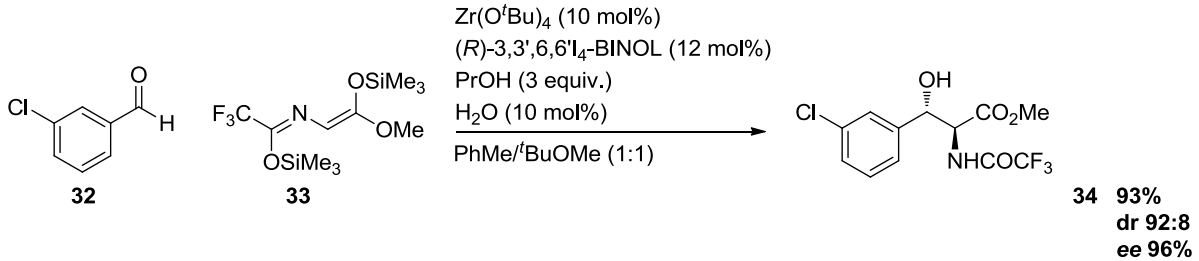
Molinski and MacMillian developed a new approach to several enantioenriched diastereomers of β-hydroxyleucine and γ-hydroxythreonine to aid in the determination of the absolute stereochemistry of the novel antifungal cyclododecapeptide, lobocyclamide B (Scheme 4).[43] Treating the lithium enolate of *N*-(diphenylmethylene)glycine *tert*-butyl ester **28**, in the presence of (-)-sparteine with isobutyraldehyde afforded both the *threo* oxazolidine **29** and *erythro* imine **30** in good yields with high levels of asymmetric induction.



Scheme 4: Aldol condensation synthesis of β-hydroxyleucine

Compounds **29** and **30** were easily separable by chromatography and both showed enantioselectivities of 60% and 56% respectively. The individual compounds were converted through to their respective diastereomer of β-hydroxyleucine. The configuration of each diastereomer was determined by comparison of optical rotations with literature values. Subsqently this methodology was applied to the synthesis of γ-hydroxythreonine isomers starting from *N*-(diphenylmethylene)glycine *tert*-butyl ester **28**, and 2-(benzyloxy)acetaldehyde, where both were obtained in 58% and 56% ee.

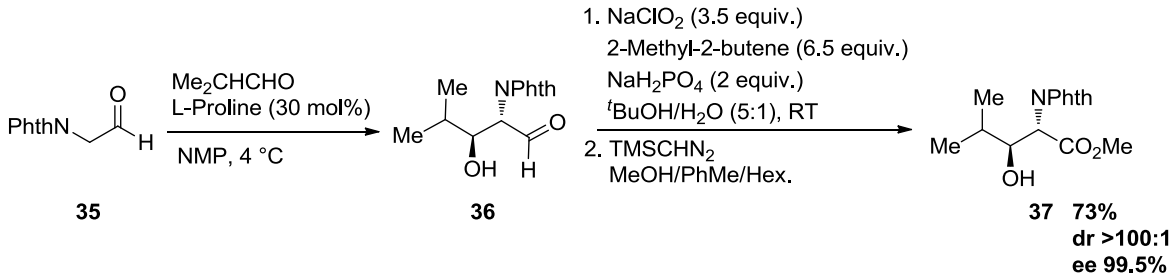
The aldol reaction between glycine-derived silicon enolates and aldehydes has been developed by Kobayashi *et al.* (Scheme 5).[44] The aldol condensation between benzaldehyde **32** and silyl ketene acetal **33** with a chiral binolzirconium catalyst, prepared *in situ* proceeded through to the *anti*-β-hydroxy α-amino acid **34** in high yield and excellent enantio- and diastereoselectivity.



Scheme 5: Aldol condensation between an aldehyde and silyl ketene acetal 33

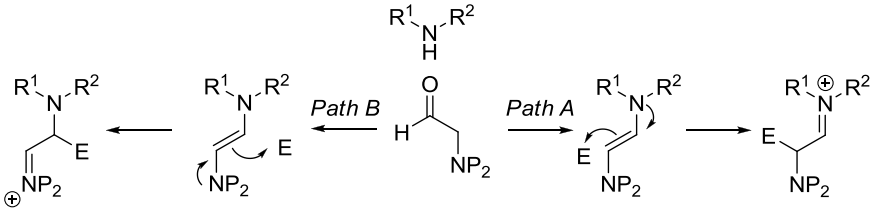
In 2004, Barbas III *et al.* reported a highly enantioselective route to *anti*-β-hydroxy α-amino acids utilizing an organocatalytic approach (Scheme 6).[45] Using L-proline, an

organocatalytic asymmetric aldol reaction between phthaloyl protected glycine aldehyde **35** and isobutyraldehyde, afforded *anti*-β-hydroxy α-amino aldehyde **36** in excellent diastereo- and enantioselectivity. Subsequent protection transformed **36** into protected *anti*-β-hydroxy α-amino ester **37** to aid with isolation and purification.



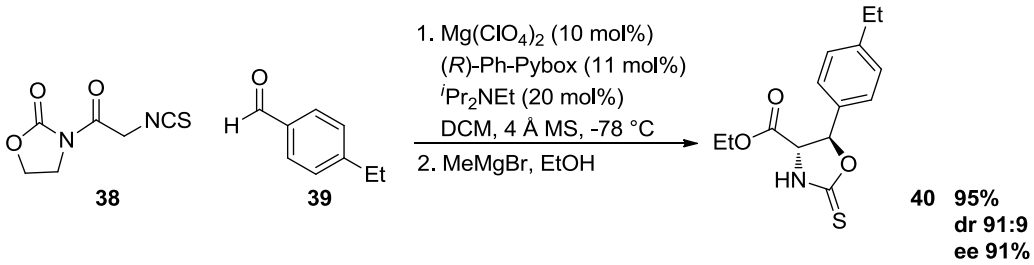
Scheme 6: Organocatalytic asymmetric aldol synthesis

The use of phthaloyl protected glycine aldehyde **35** was critical for the success of this reaction. The enamine intermediate formed between **35** and proline is capable of reacting *via* one of two pathways (Scheme 7). Protection of the amine as a phthalamide allowed for a selective enamine reaction *via* path A, when compared to other more traditional orthogonal protecting groups such as *tert*-butyloxycarbonyl (Boc) and benzoyl (Bz).



Scheme 7: Possible reaction pathways of an enamine intermediate with an electrophile

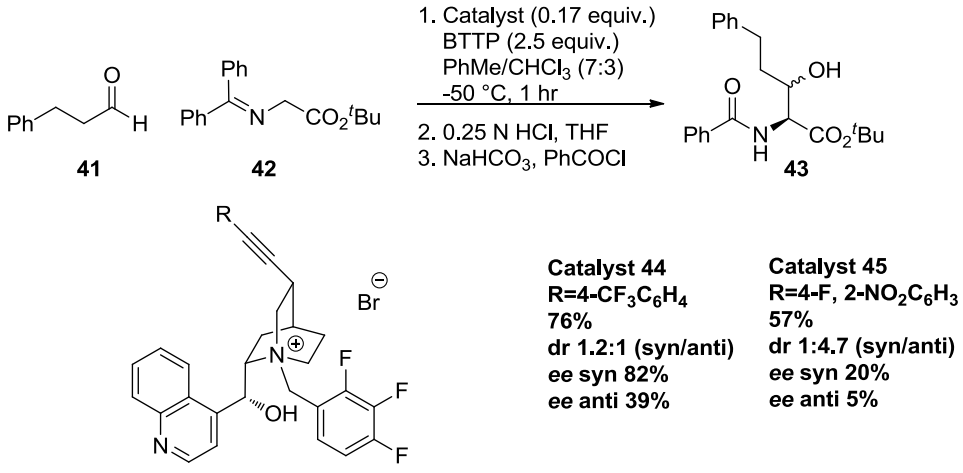
Willis *et al*. reported a highly stereoselective synthesis of protected aryl-substituted β-hydroxy-α-amino acids. (Scheme 8).[46] Using a chiral magnesium catalyst and an amine base they generated a chiral glycine enolate. This enolate undergoes enantioselective addition to an aldehyde to form a protected aryl β-hydroxy-α-amino acid in good yield with high enantioselectivity.



Scheme 8: Willis' approach to protected aryl-substituted β-hydroxy-α-amino acids

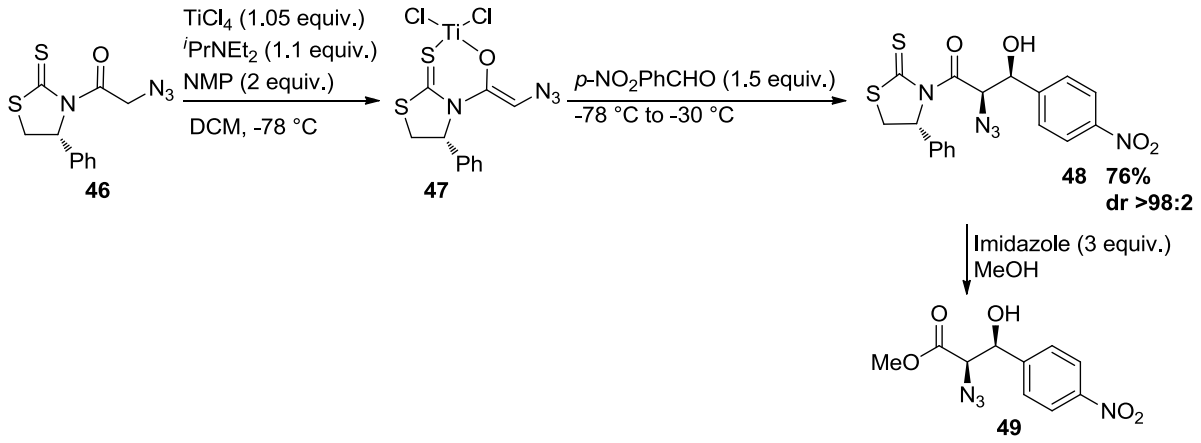
It was observed that substitution on the aryl ring had a profound impact on the diastereoselectivity. A wide range of electron rich and electron deficient substituents were tolerated in the *para* or *meta* position without significant changes to diastereo- and enantioselectivity. However, when *ortho*-tolualdehyde was used, enantioselectivity was retained, but a 1:1 diastereomeric mixture was obtained.

Castle *et al*. developed several cinchona alkaloid phase transfer catalysts based upon the Park-Jew chiral quaternary ammonium salts for use in an aldol reaction (Scheme 9).[47] These catalysts exhibited reasonable yields with modest levels of enantioselectivity; however, poor diastereoselectivity was achieved. In the aldol reaction between hydrocinnamaldehyde **41**, and *tert*-butyl glycinate benzophenone imine **42**, catalyst **44** gave the highest yield (86%), but with poor diastereomeric control. In comparison catalyst **45** gave a considerably better diastereoselectivity (1:4.7 *syn/anti*), however the desired product was obtained in a lower yield and very limited enantiomeric excess of each diastereomer respectfully (20 % *syn*; 5 % *anti*).



Scheme 9: Cinchona alkaloid catalysts approach

Franck *et al.* have recently reported a simple aldol route to access protected *syn*-β-hydroxy-α-amino acids derivatives (Scheme 10).[48]

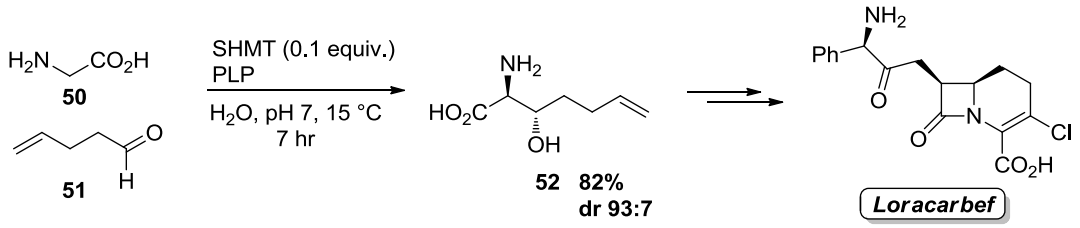


Scheme 10: Titanium mediated aldol condensation

The reaction between the stable titanium enolate **47** and an aldehyde, delivered the *syn*-aldol product **48**, in good yield and excellent diastereoselectivity. Due to the sensitivity of the product, it was subjected to methanolysis to cleave the thiocarbamate auxiliary and afford the methyl ester **49**. Notably a small degree of epimerisation occurred during this methanolysis.

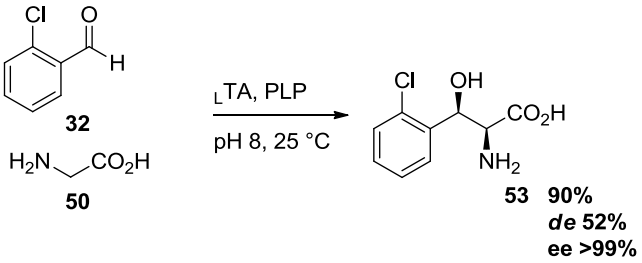
1.3.2 *Enzymatic aldol reactions*

The use of enzymes in an aldol condensation is a popular method for the formation of the β-hydroxy α-amino acid moiety. Zhang and co-workers reported the use of serine hydroxyl-methyl transferase (SHMT) as a catalyst in an aldol condensation between glycine **50** and 4-pentenal **51** (Scheme 11).[49] The enzyme successfully catalysed the reaction in good yield and excellent diastereoselectivity to obtain desired *anti*-β-hydroxy-α-amino acid **52**. Amino acid **52** was in turn used as a precursor in the total synthesis of loracarbef.



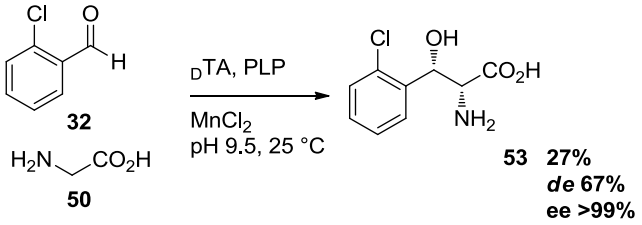
Scheme 11: SHMT catalysed aldol condensation

In 2007, Griengl *et al.* investigated the enzymatic aldol reaction between substituted benzaldehydes and glycine using L-threonine aldolase ($_L$TA) and D-threonine aldolase ($_D$TA) (Scheme 12).[50] They observed a strict requirement for glycine to be used as a donor, however a large range of aliphatic and aromatic aldehydes are tolerated. They found that $_L$TA can operate within a range of pH (6-9). Using a sterically demanding aryl aldehyde, such as 2-chlorobenzaldehyde **32**, high yield and moderate diastereomeric excess was achieved.



Scheme 12: $_L$TA catalysed aldol condensation

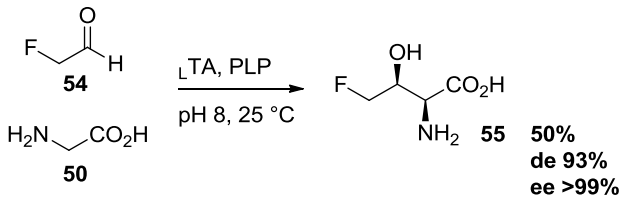
Utilizing the same substituted benzaldehydes the aldol condensation was also investigated under optimised $_D$TA conditions. In comparison, these condensations required a slightly higher and more consistent pH of 9.5 and the addition of stoichiometric manganese dichloride (Scheme 13).



Scheme 13: $_D$TA catalysed aldol condensation

Comparable diastereoselectivities were obtained for all chloro- and bromobenzaldehydes. Under the $_D$TA derived conditions, substituents on the aromatic ring had a more profound effect with *meta* substituted benzaldehydes affording higher yields and diastereoselectivites. All *ortho* substituted benzaldehydes delivered modest yields along with depleted selectivity at the β-carbon. Therefore active site $_D$TA must be more rigid and unable to occupy bulky benzaldehydes, especially *ortho* substituted variants.

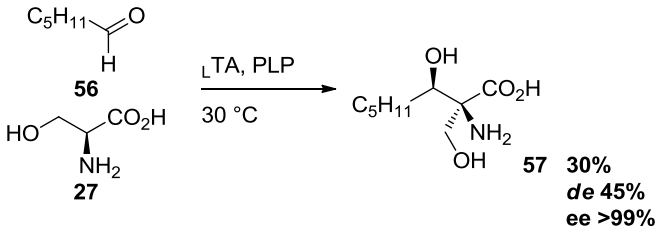
Further investigation has lead to the enzymatic aldol reaction between sterically demanding aliphatic aldehydes such as halogenated acetaldehydes or long chain aldehydes and glycine, in the formation of L-γ-threonines (Scheme 14).[51]



Scheme 14: $_L$TA catalysed aldol condensation utilizing sterically demanding aldehydes

Diastereoselectivity for the halogenated aldehydes was excellent, however the use of acetaldehyde displayed no stereoselectivity at the β-carbon. Long carbon chain aldehydes (C_7 and greater) displayed a switch in selectivity, with the *anti*-diastereomer being preferentially formed, however a much reduced yield and diastereoselectivity was obtained. The switch in selectivity occurs due to the limiting size of the hydrophobic pocket of the enzyme.

In a recent communication, Griengl *et al.* have shown the first example of a $_L$TA mediated aldol condensation using other amino acids rather than glycine (Scheme 15).[52]

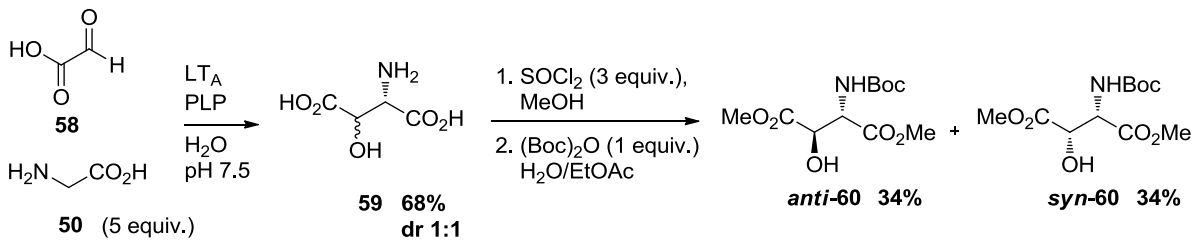


Scheme 15: $_L$TA catalysed aldol condensation utilizing serine

A strict specificity of this reaction is the requirement of unnatural D-amino acids. Along with this only three amino acids, alanine, cysteine and serine have been shown to act as suitable donors. However this publication is one of the first reports of threonine aldolase promoted enzymatic aldol condenstations in the synthesis of β-hydroxy α-amino acids containing α-quaternary centres.

Riva *et al.* investigated the use of ω-carboxy-aldehydes in a $_L$TA catalysed aldol reactions (Scheme 16).[53] Glycoxylic acid **58**, and a large excess of glycine **50**, were

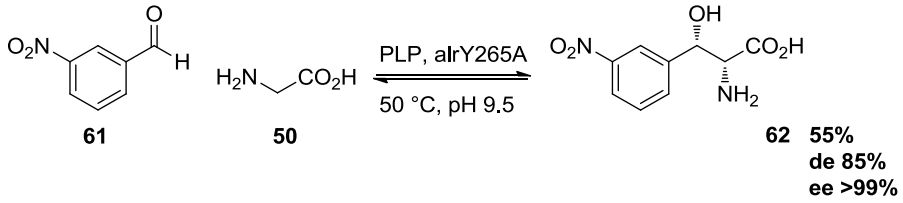
treated under optimised $_L$TA conditions for 48 hours, resulting in the formation of ω-carboxy-β-hydroxy-α-amino acid **60**.



Scheme 16: $_L$TA catalysed aldol reaction of ω-carboxy-aldehydes

Removal of excess glycine *via* ion-exchange chromatography, followed by lyophilization, allowed for the successful isolation of **59** in 68% yield as a 1:1 mixture of diastereomers. Derivatization of both diastereomers allowed separation of both isomers by flash chromatography.

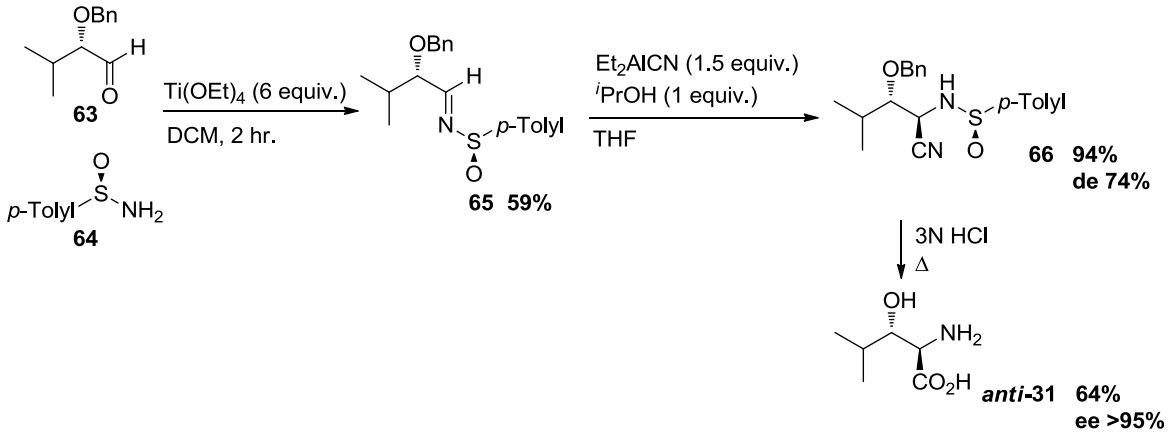
Fesko *et al.* have shown that a Y265A mutant of alanine racemase is a suitable catalyst for the synthesis of β-hydroxy-α-amino acids (Scheme 17).[54] In all cases, excellent enantio- and high diastereoselectivities were achieved, however in all examples low yields were obtained.



Scheme 17: Y265A mutant of alanine racemase catalysed aldol reaction

1.3.3 *Strecker reaction*

Another route to β-hydroxy α-amino acids was developed by Davis *et al.* in 2000.[55] An asymmetric route was established utilizing a sulfinimine-mediated Strecker reaction (Scheme 18).

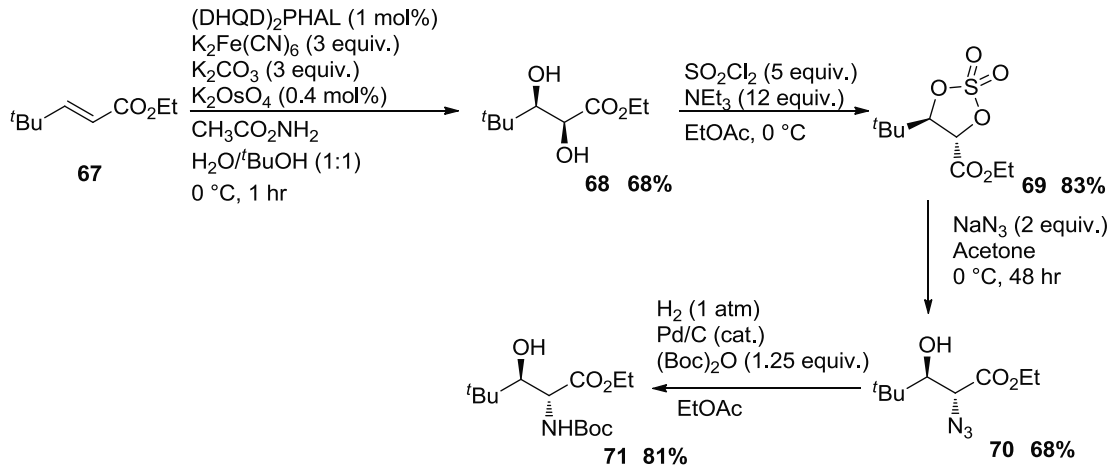


Scheme 18: Strecker reaction approach to β-hydroxy α-amino acids

Treatment of the protected aldehyde **63** with *p*-toluenesulfinamide **64** in the presence of of six equivalents of tetraethoxytitanium afforded the sulfinimine **65** in moderate yield. Upon subjection to ethylaluminium cyanoisopropoxide (generated *in situ*), the nitrile is added selectively to the *re*-face of the sulfinimine, due to the control of the sulfinyl group. The desired product **66** was afforded in excellent yield and good diastereoselectivity. Hydrolysis of the major diastereomer afforded ***anti*-31**, in 64% isolated yield and enantiomeric excess of greater than 95%. It should also be noted that the three other stereoisomers of 3-hydroxyleucine can also be synthesised *via* this method.

1.3.4 *Dihydroxylation approaches*

Alternative routes to β-hydroxy α-amino acid have utilized Sharpless enantioselective dihydroxylation methodology (Scheme 19).[56]



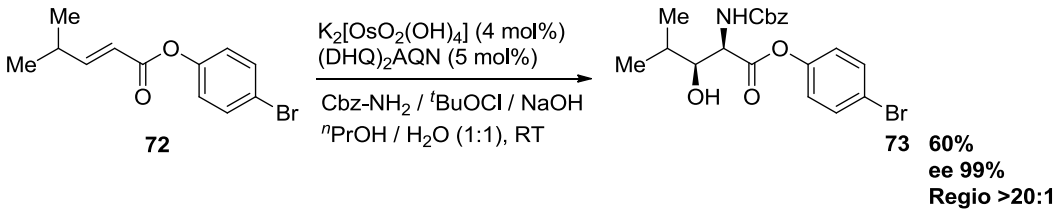
Scheme 19: Dihydroxylation approach to β-hydroxy α-amino acids

Riera utilized Sharpless' *syn*-dihydroxylation protocol with olefin **67**, to form diol **68**. Subjecting diol **68** to sulfuryl chloride in the presence of triethylamine afforded the required sulfate **69**. Ring opening with sodium azide, delivered the azido alcohol **70** in good yield. Hydrogenation followed by *in situ* boc-protection lead to the protected β-hydroxy-α-amino ester **71** in a respectable yield. This route has the advantage of delivering an enantiopure diol in one step early in the synthesis, which in turn allows for stereochemical retention through to the final product.

1.3.5 *Aminohydroxylation*

Protocols have also been developed for the synthesis of β-hydroxy α-amino acids *via* Sharpless' asymmetric aminohydroxylation of alkenes. One advantage of this protocol over the dihydroxylation methodology is the simultaneous introduction of amino and hydroxyl functionality.

Panek reported the useof this methodology in 1999, starting from α,β-unsaturated aryl ester substrates (Scheme 20).[57] Treatment of cinnamate **72** with Sharpless' aminohydroxylation conditions delivered the protected β-hydroxy α-amino acid in good yield and high enantioselectivity, however only moderate regioselectivity was achieved. After several recrystallisations, both the regio- and enantioselectivities were improved to >20:1 and 99% respectfully.



Scheme 20: Aminohydroxylation approach to β-hydroxy α-amino acids

The use of an aromatic ester was vital to obtain high regioselectivity. Using an ethyl ester cinnamate a switch in regioselectivity was observed and the α-hydroxy β-amino ester was isolated as the sole regioisomeric product. The switch in regioselectivity is thought to arise from a change in conformation of the aryl ester substrate. NOE experiments were performed, and in the case of cinnamate **72** a significant NOE was observed between the *ortho* aryl protons and the β-vinylic proton, indicating a *s-cis*

conformer (Figure 22). Since no NOE was observed between the β-vinylic proton and the ethyl group for the ethyl ester substrate **74**, this indicated a preference for the *s-trans* conformer **75**, resulting in the formation of the opposite regioisomer.

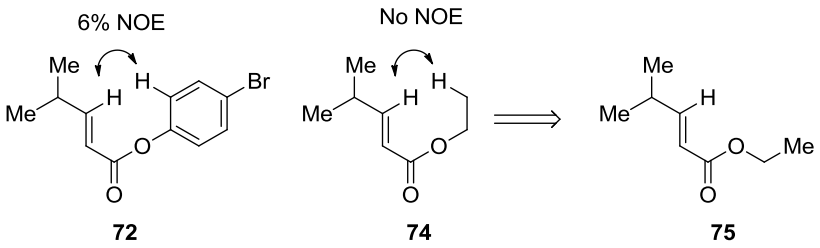
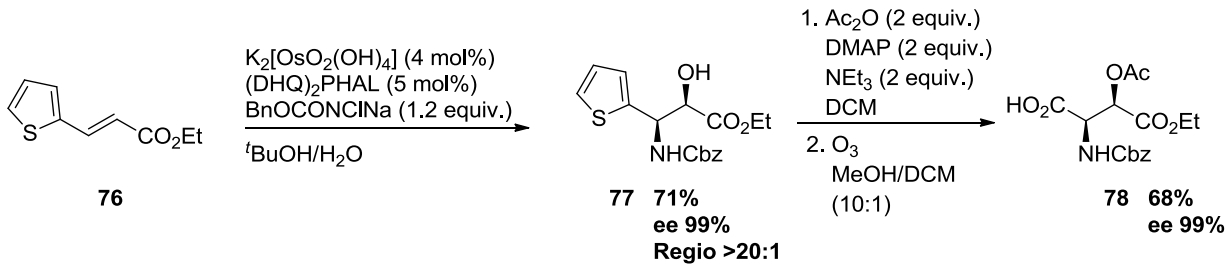


Figure 22: NOE confirmation of the change conformation between an aryl and an alkyl cinnamate

Panek also postulated that more productive π–stacking interactions between the aromatic cinnamate and the $(DHQ)_2$-AQN alkaloid ligand, also may account for the switch in regioselectivity. Further investigation using Hammett-type analysis of several *para*-substituted aromatic ester cinnamates showed that the level of enantioselectivity achieved can be directly related to the electronic properties of the olefinic substrate.

Further work within this area was published by Zhou *et al.* in 2000.[58] They showed that using heteroaromatic acrylate **76**, along with the sodium salt of *N*-chlorobenzylcarbamate under Sharpless' aminohydroxylation conditions afforded the desired β-hydroxy α-amino acid moiety **77** in a high regio- and enantioselective fashion (Scheme 21).

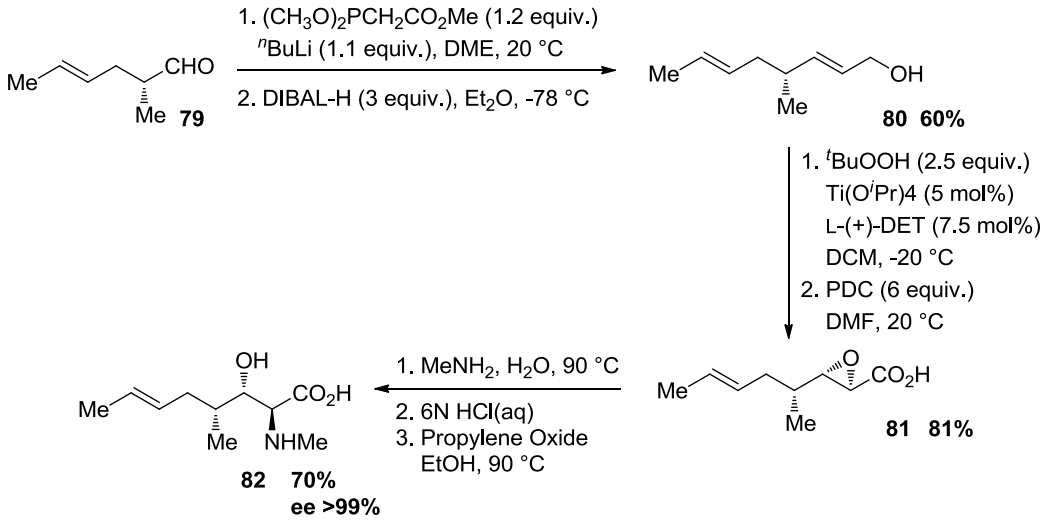


Scheme 21: Aminohydroxylation approach to β-hydroxy α-amino acids

In particular, thienyl acrylates afforded that best regioselectivity, whereas the use of furyl derivatives lead to diminished selectivity. Pyrrolyl acrylates were inert under these reaction conditions. Subsequent protection and oxidation yielded the protected β-hydroxy α-amino acid **78** in 68%.

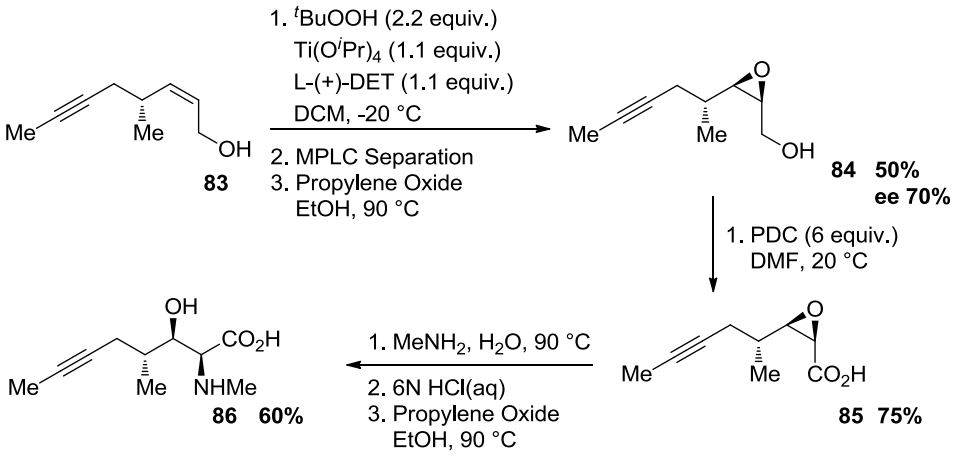
1.3.6 *Epoxidations*

Genet investigated a diastereoselective opening of epoxides with suitable nitrogen donors to afford β-hydroxy-α-amino acids (Scheme 22).[59] Wittig olefination of the enantiopure δ-γ unsaturated aldehyde **79** gives the unsaturated ester, and subsequent DIBAL-H reduction furnishes a substituted allylic alcohol **80**. Treatment with Sharpless' asymmetric epoxidation catalyst delivered the epoxy-alcohol and ensuing PDC oxidation afforded epoxy carboxylic acid **81** in 81% yield. Treatment of **81** with methylamine afforded the *N*-substituted *anti*-β-hydroxy-α-amino acid **82** in a 24 % yield over the seven steps.



Scheme 22: Epoxide opening approach to a*nti*-β-hydroxy-α-amino acids

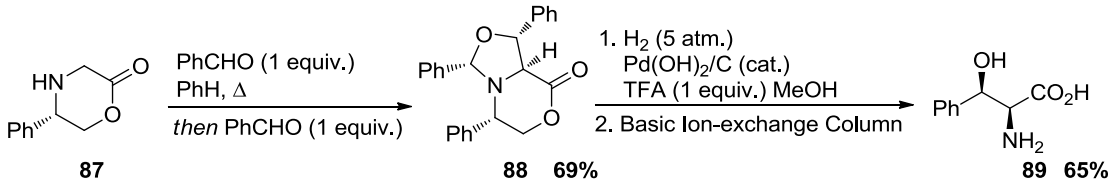
Similar methodology can be employed to obtain the *syn*-diastereomer (Scheme 23). Treating allylic alcohol **83** with Sharpless' asymmetric epoxidation catalyst delivered the *cis*-epoxy alcohol **84** after a MPLC separation in a moderate diastereomeric excess of 70%. The desired *syn*-β-hydroxy-α-amino acid **86** was obtained by using the same oxidation and regioselective epoxide opening protocols used to access the *anti*-product.



Scheme 23: Epoxide opening approach to *syn*-β-hydroxy-α-amino acids

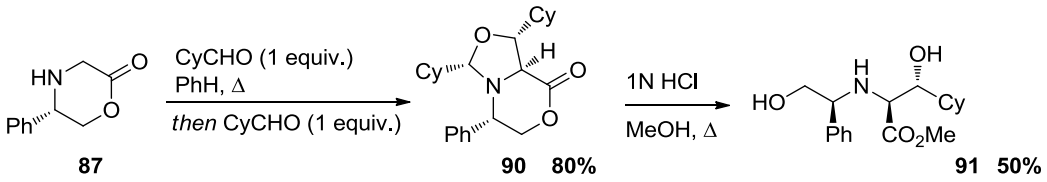
1.3.7 *Azomethine ylide*

Alker *et al*. reported the application of an azomethine ylide cycloaddition approach towards the synthesis of β-hydroxy-α-amino acids (Scheme 24).[60] Taking (5*S*)-5-phenylmorpholine-2-one **87** with an aldehyde under either Lewis acid or thermal conditions generates an azomethine ylide species as single isomer. A 1,3-dipolar cycloaddition with a second equivalent of an aldehyde delivers cycloadduct **88**, which represents a protected β-hydroxy-α-amino acid. Subjecting **88** to hydrogenolysis conditions furnishes amino acid **89**.



Scheme 24: Azomethine ylide cycloaddition approach towards the synthesis of β-hydroxy-α-amino acids

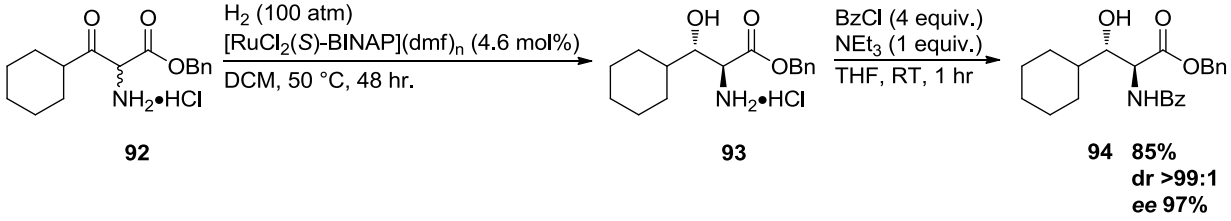
When alkyl aldehydes were subjected to the hydrogenolysis conditions, an inseparable mixture of the free amino acid and its *N*-alkylated counterpart were isolated. Upon investigation, refluxing cycloadduct **90** in methonolic hydrochloric acid led to the opening of the lactone with concomitant esterification to form the amino ester derivative **91** (Scheme 25). Both methods delivered the desired products in moderate yield.



Scheme 25: Azomethine ylid cycloaddition approach utilizing alkyl aldehydes

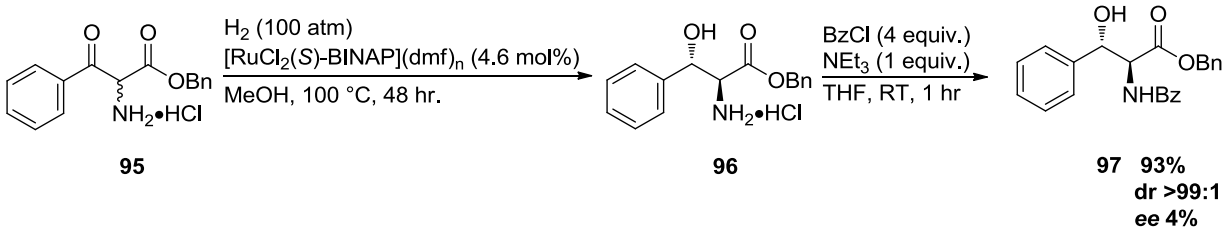
1.3.8 *Hydrogenation and dynamic kinetic resolution*

Hamada *et al.* have shown that a stereoselective synthesis of *anti*-β-hydroxy-α-amino acids can be achieved *via* dynamic kinetic resolution (DKR) (Scheme 26).[61] DKR of the β-keto-ester **92** and subsequent protection afforded the protected *anti*-β-hydroxy-α-amino acid **94** in good yield and excellent diastereoselectivity and enantiomeric excess.



Scheme 26: Hamada's dynamic kinetic resolution approach to *anti*-β-hydroxy-α-amino acids

The use of α-amino-β-keto ester substrates containing secondary carbon units α to the ketone, produced products with higher diastereo- and enantioselectivity, in comparison to primary alkyl chains. Aromatic substituents required more forcing conditions with the use of higher temperatures (Scheme 27).

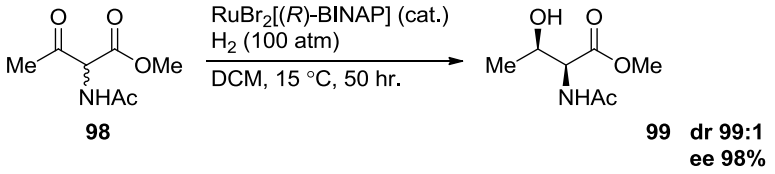


Scheme 27: DKR of aromatic derived substrates

A greater yield and excellent diastereoselectivity was achieved with aromatic substrates, however with minimal chiral induction. These results suggest that hydrogenation with the Ru–BINAP catalyst is affected by the structure at the C4 position of the α-amino-β-keto ester. Nonetheless, these represent the first example of *anti* selective hydrogenation

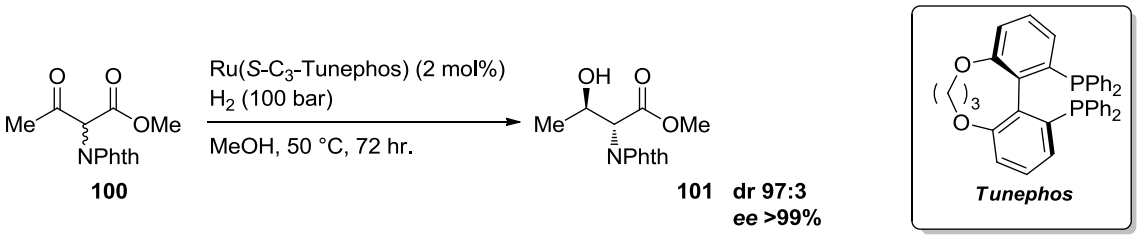
of α-amino-β-keto esters with high diastereo- and enantioselectivity through dynamic kinetic resolution.

In 1981 Noyori reported the hydrogenation of 2-acetamido β-ketoester **98** to form *syn*-protected β-hydroxy-α-amino acid **99** in excellent diastereo- and enantioselectivity (Scheme 28).[62]



Scheme 28: Noyori's hydrogenation of 2-acetamido β-ketoester

Zhang *et al.* reported in 2004 the application of a similar methodology in the synthesis of enantiomerically pure phthaloyl (Phth) protected *allo*-threonine **101** (Scheme 29).[63] Starting from α-phthalimido-β-keto ester **100**, a ruthenium catalysed dynamic kinetic resolution lead to the formation of *allo*-threonine derivatives in excellent diastereo- and enantioselectivities.

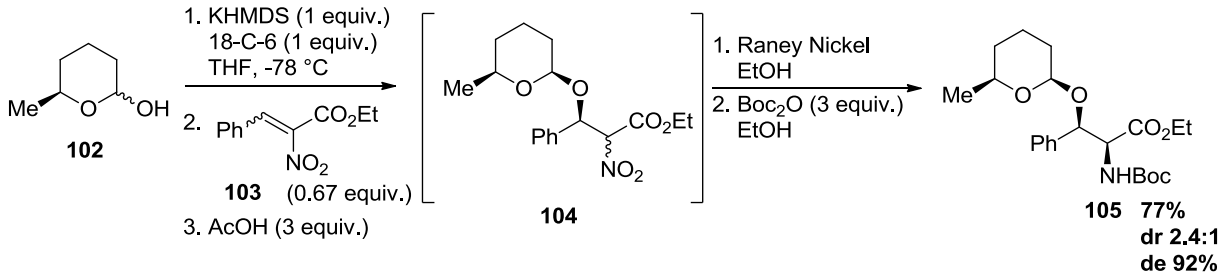


Scheme 29: Zhang's hydrogenation for the synthesis of *anti*-β-hydroxy α-amino esters

These two communications show that with careful selection of catalyst and conditions, all four isomers of threonine can be selectively synthesized.

1.3.9 *Oxy-Michael additions*

Dixon *et al*. have recently described a three step sequence to β-aryl β-hydroxy-α-amino acids, utilizing an oxy-Michael addition (Scheme 30).[64]

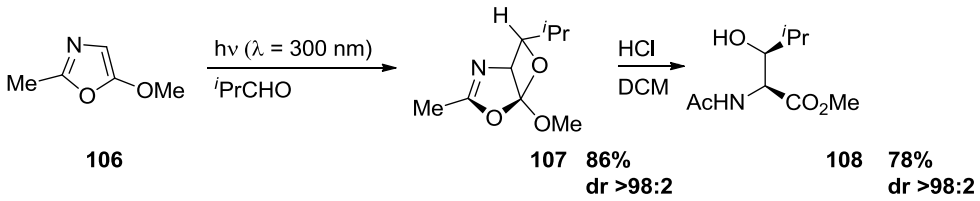


Scheme 30: Oxy-Michael addition approach towards β-hydroxy α-amino acids

Addition of KHMDS to (*S*)-6-methyltetrahydro-2H-pyran-2-ol **102**, in the presence of 18-crown-6 formed a chiral lactol alkoxide. Subsequent 1,4-addition to nitroalkene **103** gave intermediate **104** after quenching with acetic acid. Treatment of **104**, with Raney nickel and subsequent Boc-protection delivered amino ester **105** in good yield and high selectivity at the β-centre. High facial selectivity is achieved during the addition to the nitro olefin, in favour with the *syn*-diastereomer. Interestingly, the olefin geometry of the Michael acceptor has no bearing on stereoselectivity at the β-carbon.

1.3.10 *Photocycloadditions*

β-Hydroxy-α-amino acid derivatives can be prepared *via* a photoaldol route as reported by Griesbeck in 2003 (Scheme 31).[65] Photocycloadditions of 5-methoxyoxazole **106**, with an aldehyde led to bicyclic oxetane **107**. This cycloadduct was hydrolysed in aqueous acid to deliver α-acylamino β-hydroxy carboxylic acid ester **108** in high yield and diastereoselectivty.

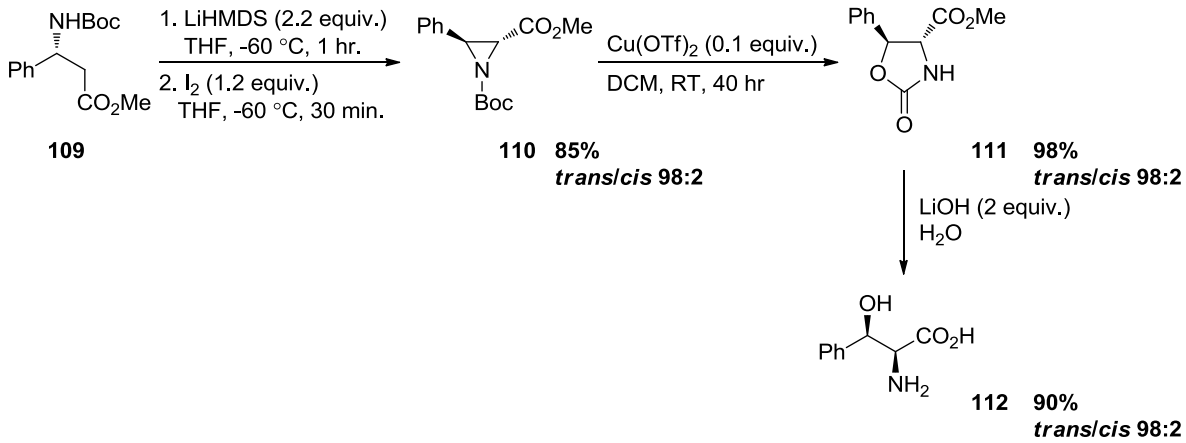


Scheme 31: Photocycloaddition approach

In all examples using both aliphatic and aromatic aldehydes, only the exo regioisomer is observed for the bicyclic oxetane. Furthermore, the formation of congested quaternary centres is feasible when starting from an oxazole containing a substitutent at the C4 position.

1.3.11 *Oxazolidinone*

The group of Tomasini has reported a novel approach to protected *syn*-β-hydroxy α-amino acids *via* 5-carboxymethyl oxazolidin-2-ones (Scheme 32).[66] Reaction of the lithium dianion of *N*-protectected β-amino ester **109** with iodine afforded the aziridine **110** in good yield and selectivity. Treatment with copper (II) triflate gave the oxazolidinone **111** in excellent yields without any loss of selectivity. The protected product can be transformed to the *syn*-β-hydroxy α-amino acid **112** by subsequent hydrolysis.



109

110 **85%** ***trans*/*cis* 98:2**

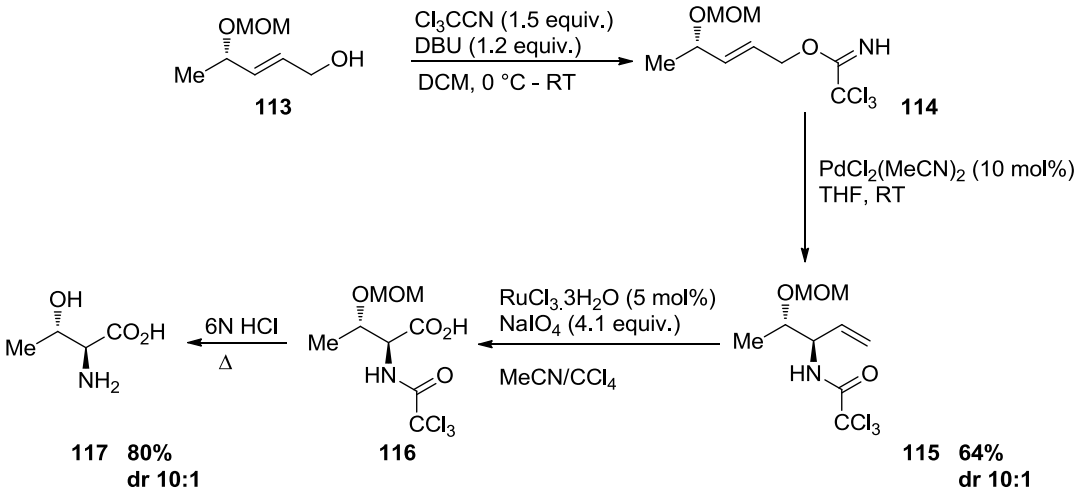
111 **98%** ***trans*/*cis* 98:2**

112 **90%** ***trans*/*cis* 98:2**

Scheme 32: Synthesis of β-hydroxy α-amino acids *via* an oxazolidinone

1.3.12 *Sigmatropic rearrangements*

Few sigmatropic approaches to the β-hydroxy-α-amino acid functionality have been reported. Sutherland *et al*. have developed a MOM-ether directed, palladium-catalysed Overmann rearrangement that proceeds to the desired product with high diastereoselectivity and good yields (Scheme 33).[67]



Scheme 33: Palladium catalysed Overmann rearrangement to β-hydroxy-α-amino acid

Starting from enantiopure α-hydroxy acids, the Overmann substrate is synthesised in six steps. Treating allylic trichloroacetamide **114** with catalytic palladium, initiates a [3,3]-sigmatropic rearrangement, delivering rearranged product **115** in good yield and moderate diastereoselectivity. Sharpless oxidation and subsequent deprotection delivered the required β-hydroxy-α-amino acid **117** without any loss of diastereoselectivity. Addition of *p*-benzoquinone improved the diastereoselectivity of the rearrangement further to 14:1, as well as suppressing any competing [1,3]-*anti*-Claisen rearrangement products being formed.

1.4 PERICYCLIC REACTIONS

Pericyclic reactions take place through concerted cyclic mechanisms, with all bond forming and breaking occurring simultaneously and without any intermediates or no formal charges being formed.[68] There are four main classes of pericyclic reactions: cycloadditions, electrocyclic reactions, group transfer reactions and sigmatropic rearrangements (Figure 23).

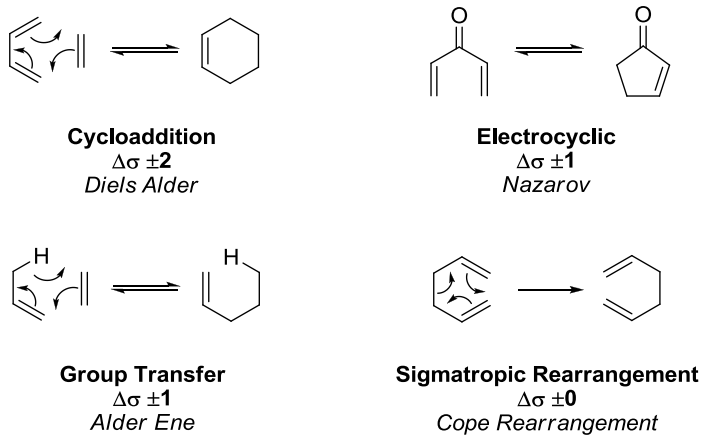


Figure 23: Examples of Pericyclic reactions

All pericyclic reactions can be classified according to the change in the number σ-bonds within the system. Cycloadditions result in the formation or loss of two σ-bonds, electrocyclic and group transfers change of one σ-bond, whilst sigmatropic rearrangements show a migration of a σ-bond, therefore a change of zero.

It was foreseen that the use of an Ireland-Claisen rearrangement as the key synthetic step in the synthesis of β-alkoxy α-amino acids would be beneficial. The versatility of the rearrangement, allowing access to either diastereomer, by changing the enolisation conditions or set alkene geometry and ease of substrate preparation were two vital aspects that made this methodology appealing. Along with mild reaction conditions and a large number of functional groups tolerated under this conditions, made the use of this [3,3]-sigmatropic rearrangement applicable for use in the formation of large complex molecules.

1.4.1 *Sigmatropic rearrangements*

During a sigmatropic rearrangement, a single σ-bond migrates from one location in a molecule to another. All sigmatropic rearrangements are assigned by a [i,j] numerical classification system, referring to the number of atoms that each end of the bond has migrated over. Examples of this numbering system can be seen in Figure 24.

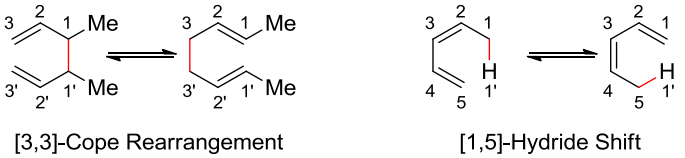
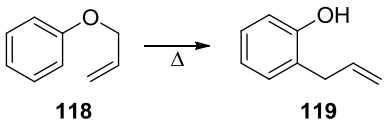


Figure 24: [i,j] Numerical classification

1.4.1.1 *Claisen rearrangement*

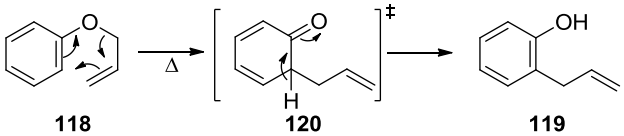
The first reported example of a sigmatropic rearrangement was published in 1912, by Claisen. He observed the thermal rearrangement of allyl phenyl ether **118** to afford allyl phenol **119** (Scheme 34).[69]



Scheme 34: Claisen rearrangement

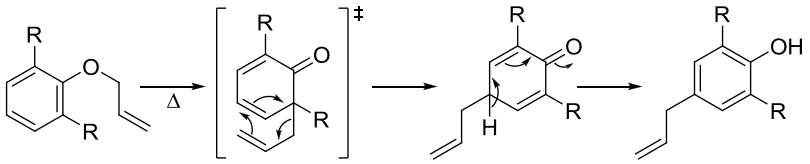
There are two main types of Claisen rearrangements; the aliphatic Claisen rearrangement and the main topic of his seminal paper the aromatic Claisen rearrangement.

The aromatic Claisen is the rearrangement of allylic aryl ethers to allylphenols upon heating. During the rearrangement an allylic shift is observed with the allylic fragment migrates to the *ortho* position of the phenolic ring. Rearomatisation of the ring to a phenol is considered to be the driving force behind this reaction (Scheme 35).[70]



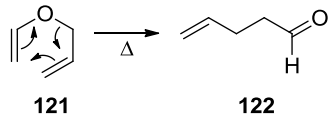
Scheme 35: Aromatic Claisen rearrangement

Should both *ortho* positions already be substituted, rearomatisation *via* this mechanism is not possible. Instead, a second migration of the allyl fragment to the *para* position *via* a [3,3]-sigmatropic Cope rearrangement is observed, followed by rearomatisation to the phenol (Scheme 36).



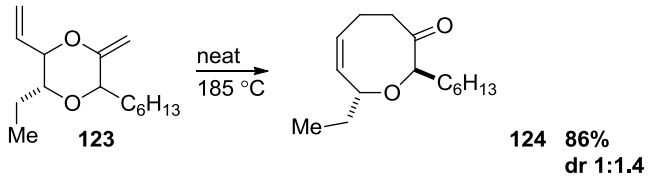
Scheme 36: Aromatic Claisen rearrangement

The aliphatic Claisen rearrangement involves the heating of an allyl vinyl ether **121** to around 200 °C, without any other reagents and leads to the formation of γ,δ-unsaturated aldehyde **122**.[69]



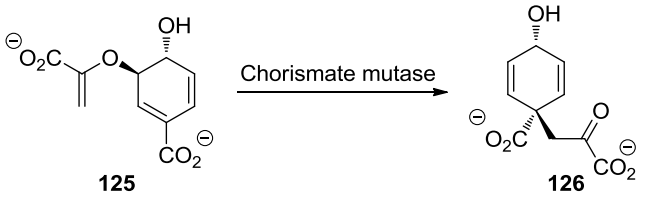
Scheme 37: Aliphatic Claisen rearrangement

In 1994, Paquette *et al.* utilized an aliphatic Claisen rearrangement to afford a ring expansion in the synthesis of 3-oxocen-7-one **124**.[71]



Scheme 38: Aliphatic Claisen rearrangement

The Claisen rearrangement is the only pericyclic reaction to be observed in a primary metabolic pathway.[72] The enzymatic aliphatic Claisen rearrangement of chorismate **125** affords prehenate **126**; a precursor for two essential amino acids; tyrosine and phenylalanine (Scheme 39).[73] Chorismate mutase, the key enzyme involved is responsible for a rate acceleration of approximately one million compared to the uncatalysed, but still facile, rearrangement.[74]



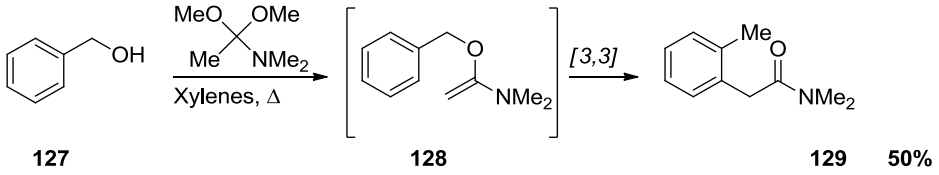
Scheme 39: Enzymatic aliphatic Claisen rearrangement

1.4.1.2 *Variants of the Claisen rearrangement*

There have been many variations of the Claisen rearrangement reported. The most popular examples of these include:

Meerwein-Eschenmoser-Claisen rearrangement

This rearrangement involves the conversion of allylic,[75-77] benzylic,[75-77] propargylic[78-79] or allenylic[80] carbinol systems. Benzyl alcohol **127** is converted to ketene *N,O*-acetal intermediate **128** upon subjection to dimethylacetamide dimethyl acetal under refluxing conditions. In turn follows a [3,3]-sigmatropic rearrangement through to γ,δ-unsaturated amide **129** (Scheme 40).

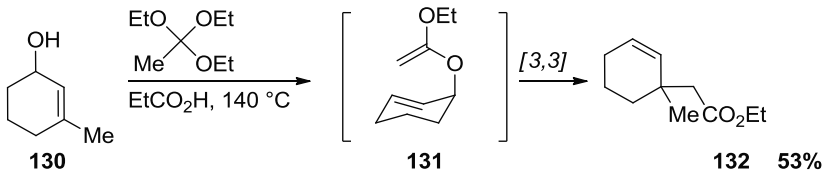


Scheme 40: Meerwein-Eschenmoser-Claisen rearrangement

The neutral conditions of this rearrangement allow for the use of sensitive substrates, as long as they are thermally stable.

Johnson-Claisen rearrangement

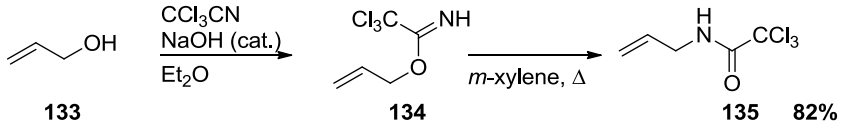
The Johnson-Claisen rearrangement is closely related to the Eschenmoser rearrangement (Scheme 41). This rearrangement proceeds *via* ketene acetal **131** which results from the condensation of an *ortho*-ester and allylic alcohol **130**.[81] The intermediate rearranges *via* [3,3]-sigmatropic rearrangement to afford γ,δ-unsaturated ester **132**.



Scheme 41: Johnson-Claisen rearrangement

Overmann rearrangement

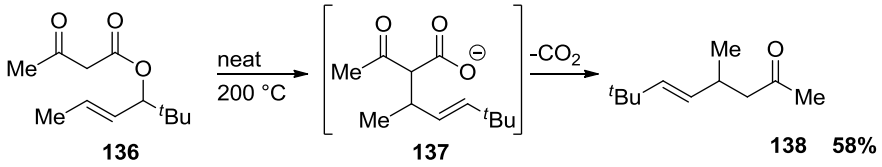
The Overmann rearrangement involves the thermal or mercuric catalysed rearrangement of allylic trichloroacetimidate **134** to afford trichloroacetamide **135**.[82] The allylic trichloroactimidates are easily prepared in one step by treating an allylic alcohol with trichloroacetonitrile in the presence of catalytic amounts of base (Scheme 42).



Scheme 42: Overmann rearrangement

Carroll rearrangement

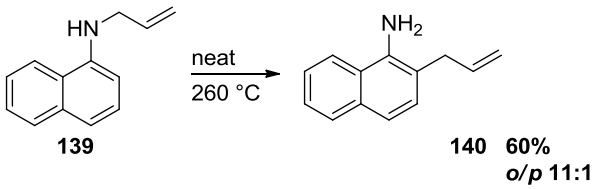
The thermal or anionic [3,3]-sigmatropic rearrangement of β-keto-allylic esters to β-keto acids is known as the Carroll rearrangement.[83-84] Ensuing decarboxylation leads to the corresponding γ,δ-unsaturated ketone.



Scheme 43: Carroll rearrangement

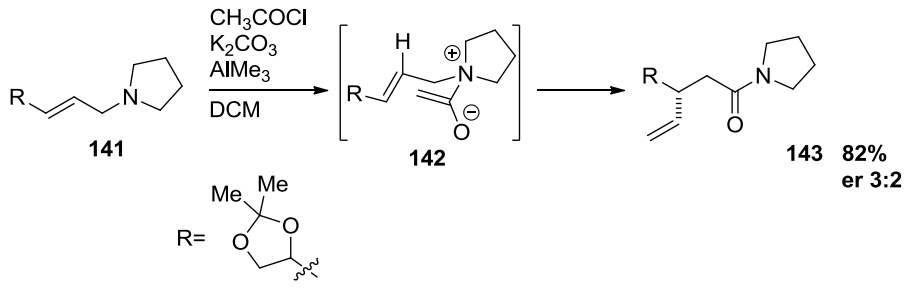
Aza-Claisen rearrangement

The Aza-Claisen utilizes a variant of the Claisen substrate which sees the substitution of the oxygen atom for a nitrogen atom.[85] The rearrangement is a thermal process and both aliphatic and aromatic substrates can be utilized under these conditions (Scheme 44).



Scheme 44: Aza-Claisen rearrangement

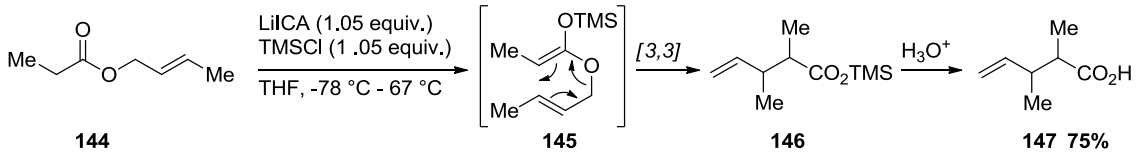
A major disadvantage of the Aza-Claisen rearrangement is the extremely harsh conditions required and as a consequence very few applications of this rearrangement have been published. The development of mild zwitterionic variants have allowed for the reduction in the temperatures used, through the use of ammonium or amide enolates (Scheme 45).[86-87]



Scheme 45: Zwitterionic aza-Claisen rearrangement

Ireland-Claisen rearrangement

The Ireland-Claisen rearrangement utilizes an allylic silyl ketene acetal as a substrate (Scheme 46).[88] Typical conditions require an allylic ester and treating this with a lithium dialkylamide base and a silyl chloride. Enolisation occurs and subsequent trapping as a silyl ketene acetal allows for a [3,3]-sigmatropic rearrangement to take place upon warming, affording a δ,γ-unsaturated carboxylic acid after protic quench. The use of the protocol developed by Ireland, allows for rearrangement to take place at significantly lower temperatures than the Claisen rearrangement.

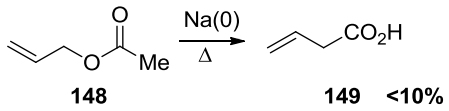


Scheme 46: Ireland-Claisen rearrangement

Ireland reported that silylation of the enolate suppressed side reactions such as decompostition *via* ketene pathways or aldol condensations occurring. It is presumed that this rearrangement is diastereoselective, since the rearrangement was presumed to go *via* a chair transition state, however no diastereoselectivity was reported in Irelands' seminal paper.

1.5 IRELAND-CLAISEN REARRANGEMENT

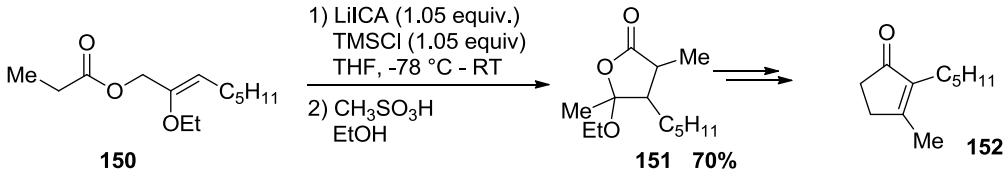
Irelands' seminal paper was not the first reported example of an ester enolate Claisen rearrangement. In 1937, Tseou and Wang reported the formation of pent-4-enoic acid **149** during an attempted condensation of allyl acetate **148** using sodium metal (Scheme 47).[89]



Scheme 47: First reported Ireland-Claisen type rearrangement promoted by sodium metal

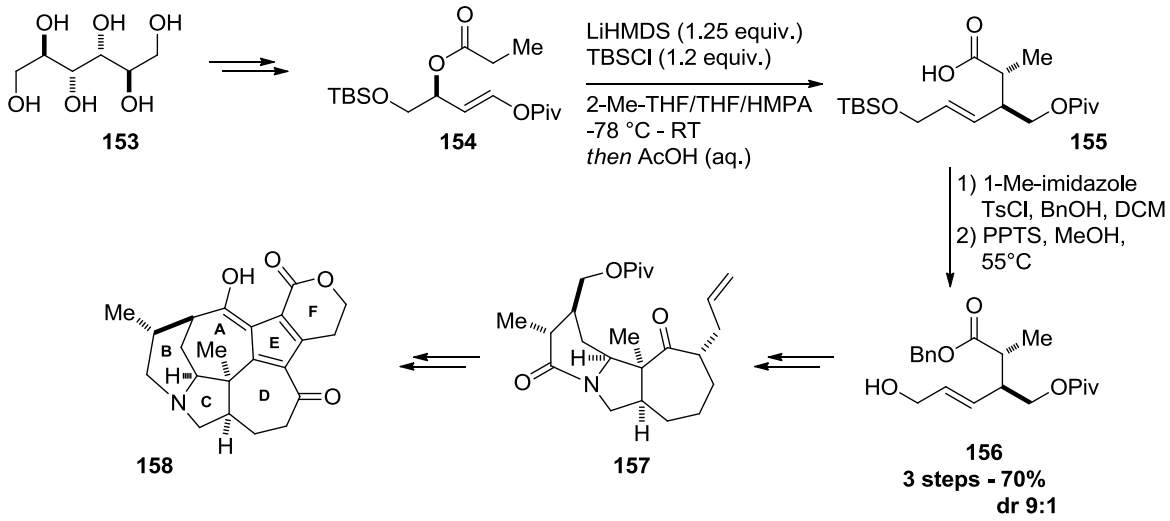
Between Tseou's publication and Irelands' first communication, multiple reports can be found in the literature of ester enolate Claisen rearrangements to the corresponding δ,γ-unsaturated carboxylic acids.[90] These reactions either employed sodium metal,[89] sodium hydride[91] or diethylaminemagnesium bromide[92] as bases to achieve the rearrangement, all however, suffered from low yields and the use of high reaction temperatures.

The Ireland-Claisen rearrangement has been widely used within the synthetic chemistry community. Ireland reported in his seminal paper the synthetic utility of the improved rearrangement by incorporating the developed methodology into the synthesis of dihydrojasmone **152** (Scheme 48).[88]



Scheme 48: Irelands' Claisen rearrangement approach to dihydrojasmine 152

Today the Ireland-Clasien rearrangement is still widely used throughout organic synthesis and this can be highlighted by the communication of Iwabuchi *et al.*(Scheme 49)[93] They used an Ireland-Claisen rearrangement in an enantioselective construction of the BCD ring system of daphnicyclidin A **158** and obtained carboxylic acid **155** in good yield. Subsequent protection of the acid as the benzyl ester, followed by silyl deprotection afforded **156** in 70% yield over the three steps and diastereomeric ratio of 9:1.



Scheme 49: An Ireland-Claisen rearrangement towards the synthesis of Daphnicyclin A 158

The popularity of the Ireland-Claisen rearrangement is due to several factors, mild reaction conditions, the ease of preparation of allylic ester substrates, and the ability to control the geometry of both the alkene fragment and the ester enolate, which in turn can lead to total diastereomeric control. If chiral allylic alcohols are used chirality transfer is possible, and also the ability to form congested quaternary centres is achievable.

1.5.1 *Stereochemical aspects of the Ireland-Claisen rearrangement*

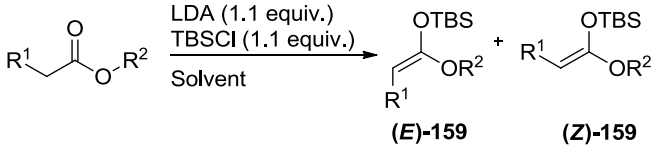
An attractive feature of the Ireland-Claisen rearrangement is the ability to consistently transfer stereochemistry to either of the newly formed sp^3 centres as well as the resultant alkene formed. Stereoselectivity is crucial to the synthesis of *syn* or *anti* pentenoic acids from their appropriate substituted allyl silyl ketene acetals. The outcome of this is determined by two factors; the geometry of both the allylic alkene and silyl ketene acetal and whether the reaction proceeds *via* a chair or boat transition state.

Enolate and silyl ketene acetal (SKA) Geometry

In 1975, Ireland reported that ester enolates of propionates and related esters could be stereoselectively generated to give either the (*E*)- or (*Z*)-SKA when trapped with *tert*-butyldimethylsilyl chloride (TBSCl) (Table 1).[94] When THF was used as a solvent, the (*E*)-SKA was predominately formed, however, upon the addition of 23% HMPA a

reversal of selectivity was observed which saw the (*Z*)-SKA prevail. (*E*)-Selectivity was generally higher, except in the case of phenyl acetates where the (*Z*)-SKA prevails.

Table 1: Solvent effects upon silyl ketene acetal geometries

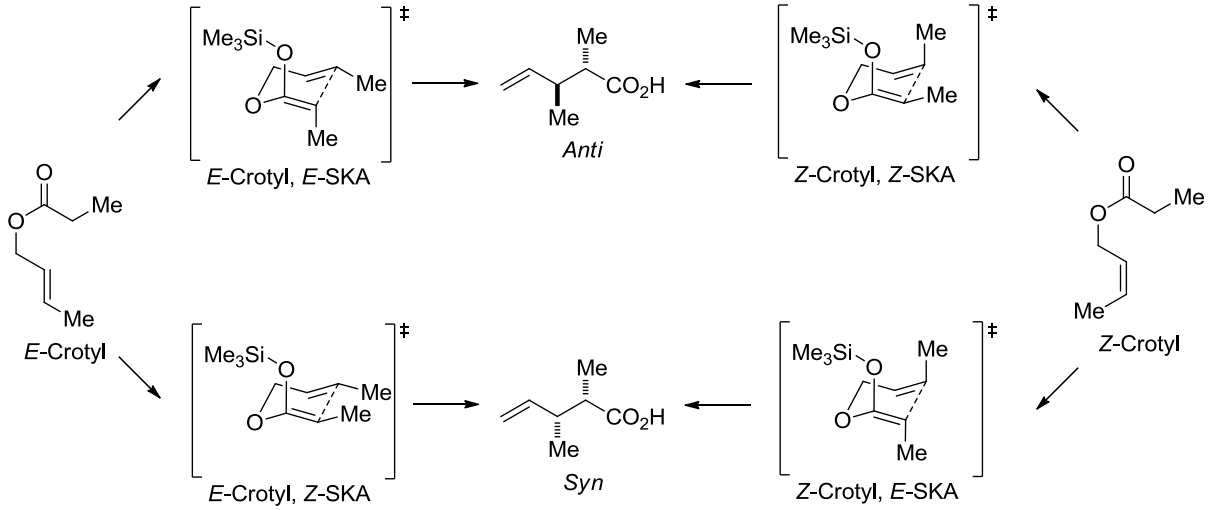


(*E*)-159 (*Z*)-159

Entry	R^1	R^2	THF ((*E*)-159 : (*Z*)-159)	THF/23% HMPA ((*E*)-159 : (*Z*)-159)
1	Et	Me	91:9	16:84
2	^{t}Bu	Me	97:3	9:91
3	Et	^{t}Bu	95:5	23:77
4	Ph	Me	29:71	5:95

Acyclic allyl silyl ketene acetals

Ireland has also demonstrated that the *anti*-2,3-dimethyl pentenoic acid isomer could be obtained by either rearrangement of the (*E*)-SKA of the (*E*)-crotyl propionate or from the (*Z*)-SKA of the (*Z*)-crotyl propionate.[1,83,88,95] It was noted that comparable levels of diastereoselectivity was achieved no matter whether the (*E*)-crotyl, (*E*)-SKA or the (Z)-crotyl, (Z)-SKA route was utilized. Conversely, the *syn*-acid could be obtained from the (*E*)-SKA of the (*Z*)-crotyl propionate or the (*Z*)-SKA of the (*E*)-crotyl propionate. This time however the diastereoselectivites increased from 5:1 to 8:1 (Scheme 50).

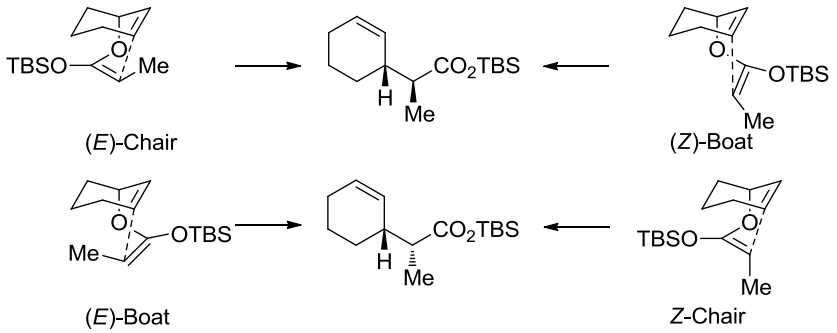


Scheme 50: Acyclic allyl silyl ketene acetals

These stereochemical outcomes are consistent with the rearrangement proceeding through a chair transition state. Computational analysis has calculated the energy difference between a chair and boat transition state to be 2.3 kcal/mol, therefore showing that for acyclic substrates, the chair transition state is preferential.[96]

Cyclic allyl silyl ketene acetals

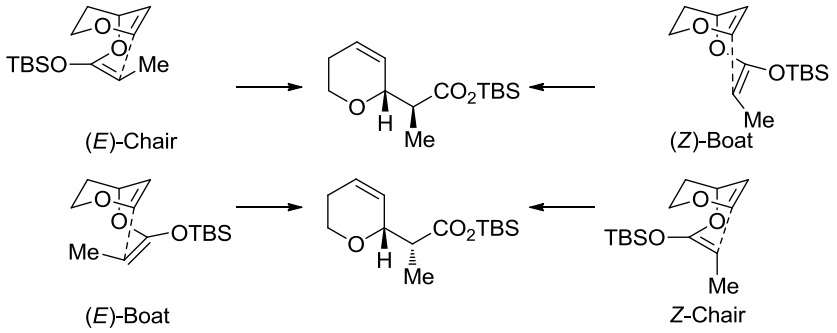
The rearrangement of cyclic substrates can occur through either chair or boat transition states. It has been reported by Ireland has that this preference is highly dependant on ring size, ring constitution and substituent stereochemistry.[97-98] In 1981, Bartlett and Pizzo reported that cyclohexyl propionates rearrange to the same major isomer under both sets of Irelands' conditions (Scheme 51).[99] They concluded that the (*E*)-SKA rearranges *via* a chair-like transition state, whereas the (*Z*)-SKA goes through a boat-like transistion state. This has more recently been supported by further computational analysis by Houk *et al*.[96]



(*E*)-Silyl Ketene Acetal: Chair/Boat = 85:15
(*Z*)-Silyl Ketene Acetal: Chair/Boat = 25:75

Scheme 51: Cyclic silyl ketene acetals

In the case of dihydropyran- and dihydrofuran-derived allylic esters the boat transition state is favoured, irrespective of the silyl ketene acetal geometry (Scheme 52).[98] There have been several proposals put forward to this, including that a greater C-O bond cleavage in the transition state reduces steric interactions between the methyl group and the ring. Greater bond cleavage results in a more polarized transition state and due to the improved overlap of the allyl fragments in a boat transition state, dihydropyran- and dihydrofuran-derived allylic esters will preferentially rearrange *via* a boat transition state. However this theory has yet to be fully elucidated and no supporting computational analysis has been reported.



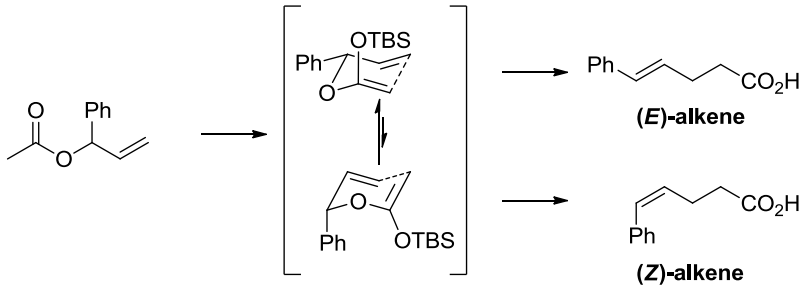
(*E*)-Silyl Ketene Acetal: Chair/Boat = 29:71
(*Z*)-Silyl Ketene Acetal: Chair/Boat = 14:86

Scheme 52: Geometries of dihydropyran allylic silyl ketene acetals

Alkene stereochemistry

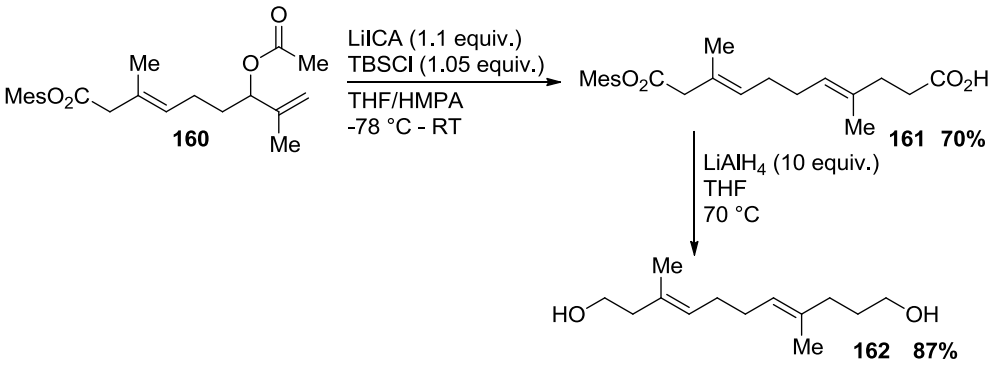
The rearrangement of allylic esters derived from primary alcohols leads to the formation of terminal alkenes. If the alcohol precursor is secondary or tertiary then there is the possibility of the formation of two alkene isomers. Again, due to the highly ordered

transition state for acyclic systems, the stereochemistry of these alkenes is highly predictable in secondary carbinol derived esters (Scheme 53).



Scheme 53: Alkene stereochemistry

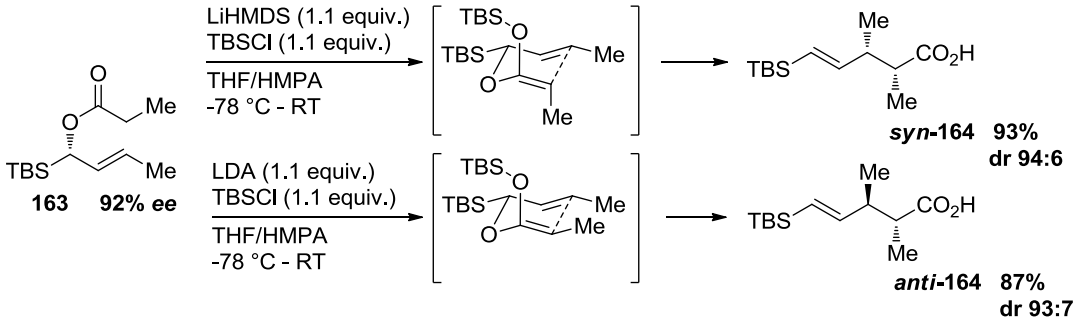
The larger C4 substituent will be placed in a *pseudo*-equatorial position. This is illustrated by Katzenellenbogen in the synthesis of butterfly pheromone **162**, in which the (*E*)-alkene was selectively formed (Scheme 54).[100]



Scheme 54: Katzenellenbogen synthesis of butterfly pheromone 162

Allylic esters possessing one stereocentre: absolute stereocontrol

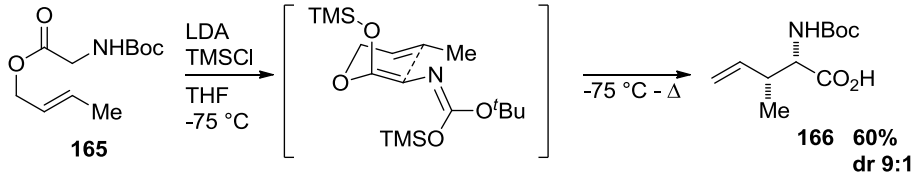
Absolute stereocontrol can be achieved in an Ireland-Claisen rearrangement when a enantiopure chiral secondary alcohol is used. This will enable the transfer of chirality from the carbinol centre to the newly formed stereocentre(s) at C(2) and/or C(3) of the pentenoic acid product. The first example of this was demonstrated by Ireland utilizing a bulky TBS crotyl propionate (Scheme 55).[101]



Scheme 55: Absolute stereocontrol

1.5.2 *Glycinates and other higher amino esters*

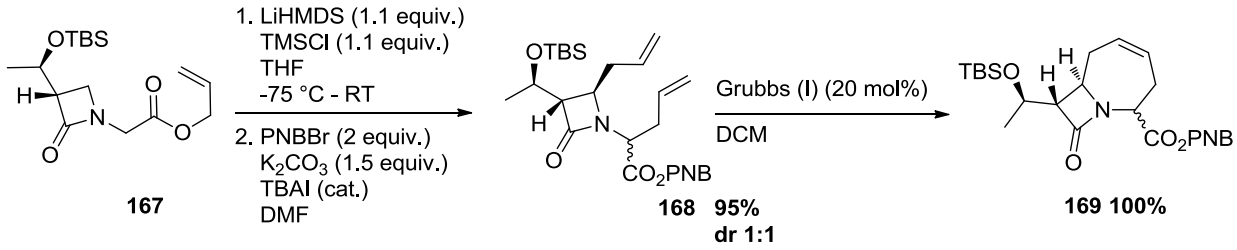
Barlett and Barstow reported the first synthesis of α-amino acids using an Ireland-Claisen rearrangement (Scheme 56).[102]



Scheme 56: Rearrangement of amino acid derived allylic esters

Barlett observed that in all cases, except for crotyl glycinate **165**, the rearrangement was successful with or without the use of a silylating agent.

Barrett *et al.* also utilized an Ireland-Claisen rearrangement containing an allyic amino ester substrate combined with alkene metathesis in the synthesis of bicyclic β-lactams (Scheme 57).[103] The rearrangement proceeded in excellent yield, however no diastereoselectivity was achieved. The ring closing metathesis proceeded smoothly to afford **169** in a quantitative yield using 20 mol% of Grubbs first generation catalyst.



Scheme 57: Use of an Ireland-Claisen rearrangement in the syntheis of bicyclic β-lactam 169

Chelated enolate Claisen rearrangements

One other method for suppressing competing side reactions and ensuring diastereoselective control in the Ireland-Claisen rearrangement include the formation of a metal enolate. Should a heteroatom with a free pair of electrons or a formal negative charge be present either α- or β- to the ester, then metal chelation between the heteroatom, the enolate and a Lewis acidic metal is possible. This gives rise to either a five- or six-membered chelate, and these in turn afford highly selective formation of (*Z*)-enolate, irrespective of the addition of HMPA (Figure 25).

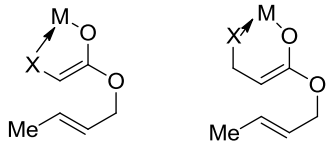
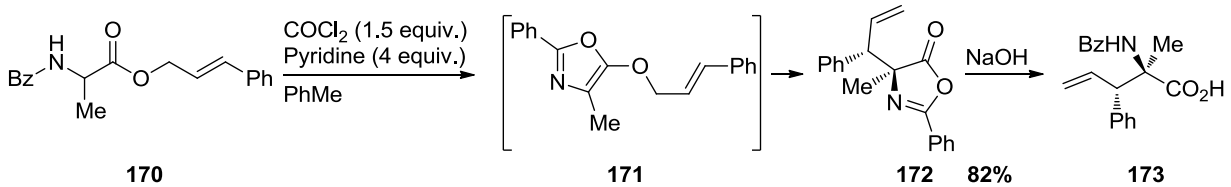


Figure 25: Five and Six membered metal chealtes

Chelate formation generally results in stabilization of the enolate, and allows for direct rearrangement.[104] However, silylation and then rearrangement of the silyl ketene acetal, according to Irelands' protocol is still possible.

The rearrangement of *N*-protected amino allylic esters has been reported by Steglich *et al.* in 1975 (Scheme 58).[105] Subjecting *N*-benzoyl amino acid allylic ester **170** to dehydrating agents (as in this case phosgene) results in the formation of oxazole intermediate **171**, which in turn rearranges to afford allyloxazolinone **172**. The fixed geometry of the alkene in the oxazole ring gives a strong preference for a chair-like transition state leading to high diastereoselectivies. Subsequent hydrolysis afforded the α-alkylated amino acid **173**.



170 **171** **172** **82%** **173**

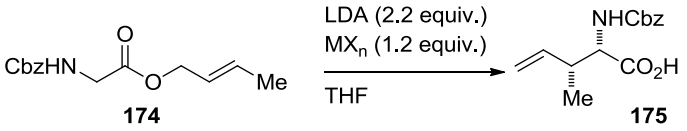
Scheme 58: Rearrangement of *N*-protected amino allylic esters

However, this method is limited to only *N*-benzoyl protected amino acid esters, other commonly used nitrogen protecting groups do not allow the cyclization to the

intermediate allyloxazolinone, therefore the required substrate for the rearrangement to occur is not achieved.

In 1994, Kazmaier investigated the effect of metal salts in the Ireland-Claisen rearrangement of *N*-benzyloxyglycine crotyl ester **174** (Table 2).[2,104,106-113]

Table 2: Effect of chelating metals on diastereoselective control



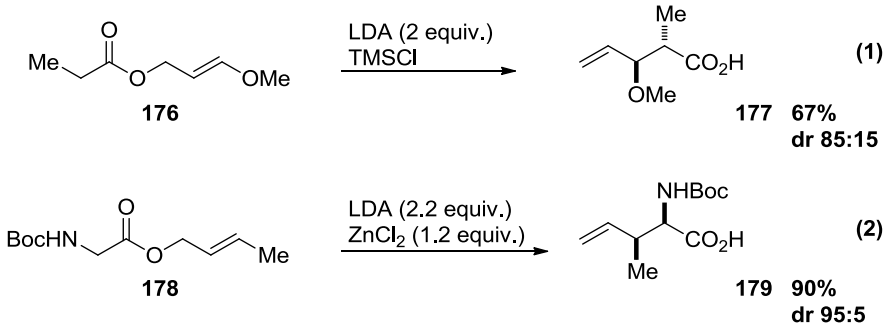
Entry	MX_n	Yield (%)	dr (*syn*:*anti*)
1	None	0	-
2	$ZnCl_2$	90	95:5
3	$CoCl_2$	78	93:7
4	$MgCl_2$	85	91:9
5	$Al(O^iPr)_3$	75	90:10
6	$Ti(O^iPr)_4$	50	90:10
7	Me_2SiCl_2	50	85:15
8	Me_3SiCl	60	83:17

The corresponding lithium enolate (Entry 1) did not show any signs of rearrangement due decomposition side reactions occuring. In contrast, the addition of chelating metal salts allowed for successful rearrangement. The chelated enolates were more stable than their lithium counterparts, and therefore lead to successful rearrangement. Zinc dichloride (Entry 2) afforded the best result in terms of both yield and diastereoselectivity, however magnesium dichloride (Entry 4) gave comparable results in other substrates. Interestingly, it was shown that metal enolates were superior to silyl ketene acetals (Entries 7 & 8) both in terms of yield and diastereoselectivity.

CHAPTER 2 DEVELOPMENT OF AN IRELAND-CLAISEN VARIANT

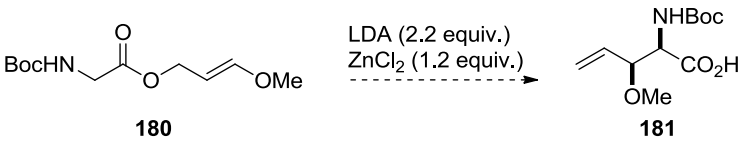
2.1 BACKGROUND

Prior to commencing this research, two key rearrangements reported in the literature were significant. Firstly, Ireland's allylic enol ether **176** was shown to rearrange to the *anti*-β-methoxy carboxylic acid **177** in good yield and diastereoselectivity (Scheme 59, equation 1).[1] The second rearrangement was reported by Kazmaier, where he demonstrated the *syn*-selective rearrangement of allylic amino ester **178** to α-substituted amino acid **179** *via* a metal chelated enolate in high yield and with excellent diastereoselectivity (Scheme 59, equation 2).[2]



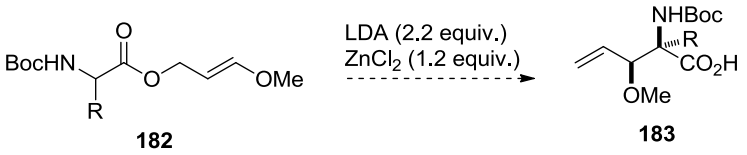
Scheme 59: Ireland's allylic enol ether and Kazmaier's allylic amino ester rearrangements

It can be envisaged that a combination of Ireland's allylic enol ether and Kazmaier's amino ester fragments would provide a suitable substrate **180**, that upon treating under Kazmaier's optimised protocol, would rearrange to afford *syn* selective β-alkoxy α-amino acids (Scheme 60).



Scheme 60: Proposed Ireland-Claisen synthesis of β-hydroxy α-amino acids

Furthermore, the use of Kazmaier's protocol has also been shown to be effective in the formation of quaternary centres in a highly diastereoselective fashion, when using α-substituted amino acids as part of the allylic amino ester substrate (Scheme 61).[108]



Scheme 61: Proposed Ireland-Claisen synthesis of β-hydroxy α-amino acids containing α-quaternary centres

Significantly amino acids containing quaternary α-carbons are an important class of non-proteinogenic amino acids, and have been gathered a significantly amount of interest in the synthetic community due their activity towards enzyme inhibitors.[114]

The use of protected allylic enol ethers, such as benzyl or *p*-methoxybenzyl, would enable the selective cleavage of these groups to form the free β-hydroxy α-amino acid moiety seen in many important biologically active products such as kaitocephalin **7** or to allow for further synthetic transformations such as a β-lactonization as seen in salinosporamide A **20** (Figure 26).

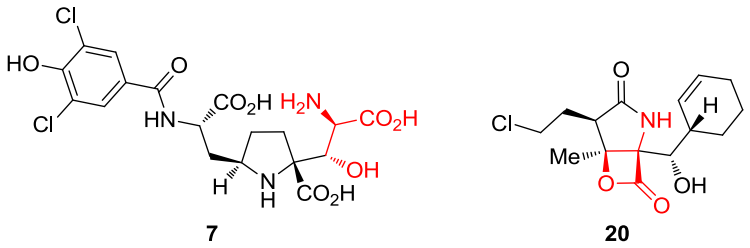
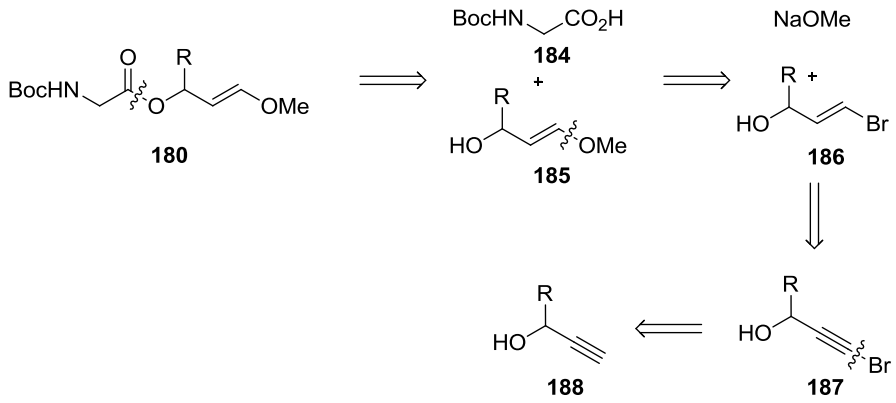


Figure 26: Examples of natural products for the incorporation of β-hydroxy α-amino acids

2.2 IRELAND-CLAISEN SUBSTRATE SYNTHESIS

2.2.1 *Retrosynthesis*

With a clearly defined substrate **180** identified, retrosynthetic analysis identified readily available commercial starting precursors (Scheme 62).

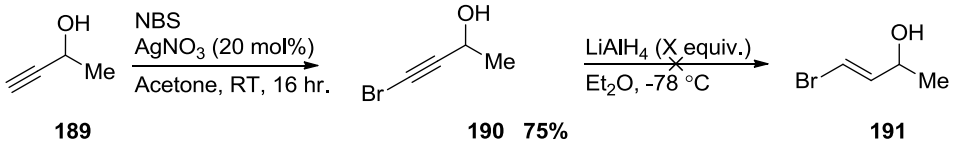


Scheme 62: Substrate retrosynthetic analysis

The retrosynthesis takes us back to one main, readily available class of alcohols such as **188**. Bromination followed by reduction affords the bromo allylic alcohol **186**. A copper promoted cross coupling between **186** and a suitable alkoxide coupling partner, such as sodium methoxide would deliver the required alkoxy allylic enol ether **185**. Subjecting **185** and *N*-Boc glycine **184** to carbodiimide coupling conditions would then afford the required allylic amino ester for the rearrangement in four steps.

2.2.2 *Forward synthesis*

Starting from 3-butyn-2-ol **189**, bromoacetylene **190** was synthesised utilizing a silver nitrate catalysed, *N*-bromosuccinimide (NBS) bromination, adapted from the method reported by Hofmeister, yielding **190** in 75% (Scheme 63).[115]



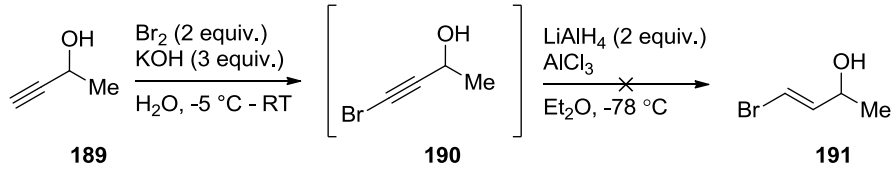
189 **190** **75%** **191**

Scheme 63: Attempted synthesis of vinyl bromide 191

Several attempts to reduce the alkyne utilizing lithium aluminium hydride based protocols all yielded an intractable mixture of compounds, of which were sensitive to column chromatography.

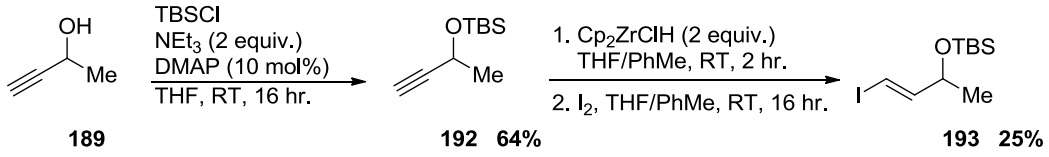
A sequential method of bromination followed by hydride reduction was reported by Polt *et al.* in 1999.[116] Subjecting **189** to bromination utilizing potassium hypobromide (generated *in situ*), formed bromoacetylene **190.** Without isolation or purification, **190** was treated with lithium aluminium hydride in the presence of stoichiometric aluminum

trichloride to form vinyl bromide **191**. The obtained product was not as desired, instead only bromoacetylene **190** was isolated indicating that reduction had not occurred (Scheme 64).



Scheme 64: Attempted synthesis of vinyl bromide 191

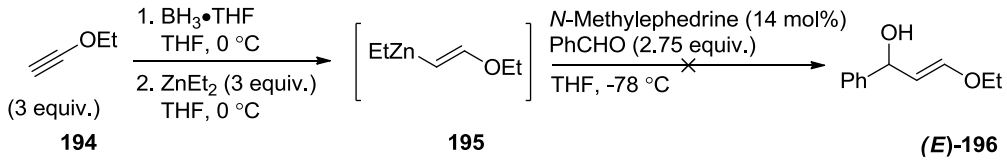
Chemin *et al.* had shown that (*E*)-vinyl iodides could be synthesised employing hydrozirconation of terminal alkynes.[117] Again starting from 3-butyn-2-ol **189**, protection of the hydroxyl group as the TBS ether under standard protocols delivered the protected alcohol **192**.[118] Hydrozirconation utilizing Schwartz reagent (synthesised from zirconocene dichloride and lithium aluminium hydride) followed by iodolysis delivered the required protected (*E*)-vinyl iodide **193** (Scheme 65).



Scheme 65: Synthesis of vinyl iodide 193

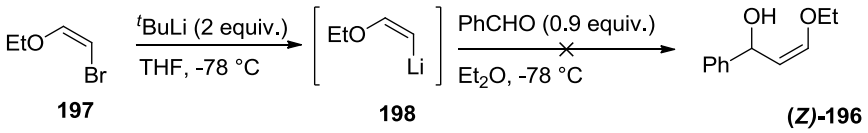
Vinyl iodide **193** was obtained in low yield and was extremely sensitive to purification. Due to the sensitivity and the limited quantities of the product obtained, deprotection of the silyl ether was not investigated. Several attempts to substitute the iodine for bromine, to form the vinyl bromide *via* this procedure were also unsuccessful.

In 2005, Walsh *et al.* published a synthetic route to alkoxy allylic enol ethers starting from terminal alkoxyalkynes.[119] Subjecting ethoxy acetylene **194** to hydroboration conditions using borane THF complex, followed by transmetalation with diethyl zinc afforded vinyl zinc **195** *in situ*. A 1,2-addition to benzaldehyde in the presence of *N*-methyl ephedrine should yield allylic enol ether **(*E*)-196** (Scheme 66). However, even though complete consumption of starting material was observed by thin layer chromatography (TLC) analysis; none of the desired product was isolated from the complex reaction mixture.



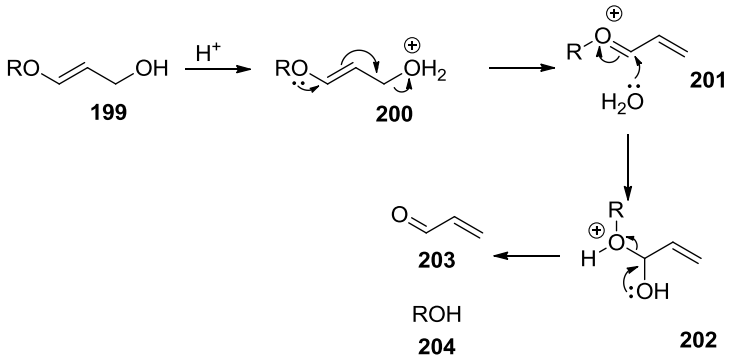
Scheme 66: Attempted synthesis of allylic enol ether (*E*)-196

Madduluno *et al*. reported the addition of lithiated enol ethers to aldehydes.[120] Lithium halogen exchange using (*Z*)-1-bromo-2-ethoxyethene **197** affords the vinyl lithium **198**, before the 1,2-addition to benzaldehyde affording alkoxy allylic enol ether **(*Z*)-196** (Scheme 67). Once again, none of the required product was observed and due to the use of expensive starting materials alternative routes into the required allylic enol ethers were pursued.



Scheme 67: Attempted synthesis of allylic enol ether (*Z*)-196

Due to the inability to synthesise these alkoxy allylic enol ethers we thought about the reactivity of these compounds. In acidic media, these compounds act as vinylogous hemiacetals, with protonation of the hydroxyl group leading to elimination of water leading to oxonium cation **201**. A 1,2-addition of the water into the oxonium cation **201** forms hemiacetal **202**, which in turn decomposes to form acrolein **203** and an alcohol (Scheme 68).

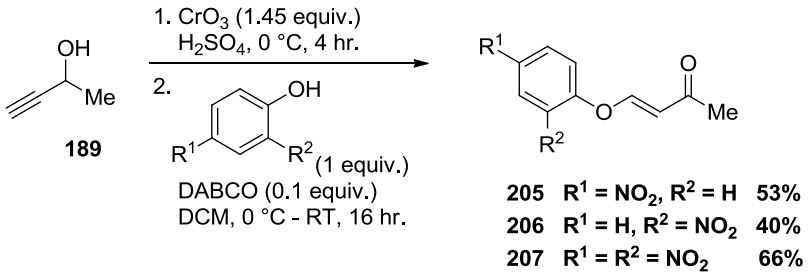


Scheme 68: Decomposition of allylic enol ethers in acidic media

It was proposed that reducing the ability of the allylic enol ethereal oxygen, to donate a lone pair of electrons into the π-system of these compounds could potentially increase their stability and the ease of synthesis. The use of aromatic rings containing electron

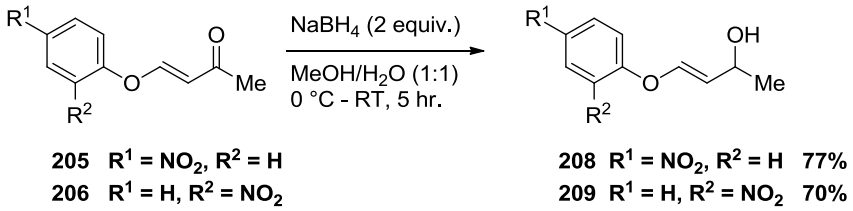
withdrawing groups should reduce the donation of these lone pair of electrons by drawing the electron density into the aromatic π-system.

Liang *et al.* had shown that a 1,4-addition of various oxygen nucleophiles to activated alkynes, such as methyl propiolate, when catalysed by 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded solely (*E*)-alkenoic acid esters.[121] But-3-yn-2-ol **189** was therefore subjected to a Jones oxidation to afford the volatile but-3-yn-2-one. Without isolation, but-3-yn-2-one, was subjected to the 1,4-addition protocol developed by Liang using *p*-nitrophenol, *o*-nitrophenol or 2,4-dinitrophenol as the oxygen nucleophile to afford the required desired product as a single isomer (Scheme 69).



Scheme 69: Synthesis of 4-aryloxy but-3-en-2-ones

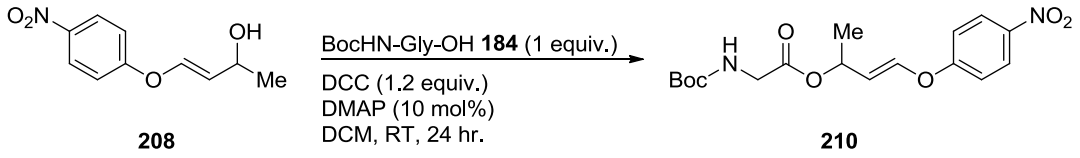
Subsequent chemoselective reduction of the carbonyl was achieved, in moderate yield using sodium borohydride (Scheme 70). Purification of the obtained product was now achievable by recrystallisation and as a result, the aryloxy allylic enol ethers were bench stable for several weeks.



Scheme 70: Reduction of 4-aryloxy but-3-en-2-ones

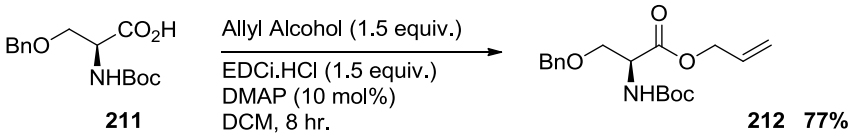
Kazmaier has shown a large range of protected amino esters successfully rearrange *via* metal chelates to the desired α-amino acids, with *tert*-butyl carbamate (Boc) protected glycine displaying excellent results.[2] Taking aryloxy allylic enol ether **208** and *N*-boc

glycine under a typical dicyclohexylcarbodiimide (DCC) coupling protocol led to the formation of the required allylic amino ester as judged by ^{1}H NMR analysis of the crude reaction mixture (Scheme 71).[122]



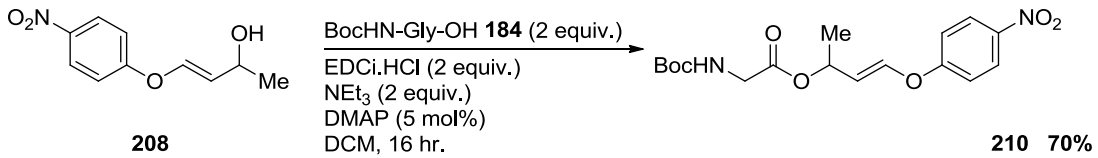
Scheme 71: Attempted synthesis of 210 using DCC

Although crude ^{1}H NMR suggested the formation of the desired allylic amino ester, purification proved difficult and none of the desired product was isolated. It was seen that the amino ester substrate was sensitive to flash chromatography even using deactivated silica or basic grade alumina. Therefore, purification *via* this method to remove the excess DCC and the formed urea by-product was unsuitable. Further reviews of the literature showed that Sarabia *et al.* were able to synthesis the allylic amino ester **212** in good yield using *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCi.HCl) as the coupling promoter (Scheme 72).[123]



Scheme 72: Sarabias synthesis of 212 using EDCi

The major benefit of switching EDCi is that excess EDCi and the urea formed during the reaction are both water soluble. Therefore, purification can be achieved by using acid/base washes rather than flash chromatography thus avoiding the degradation previously observed. Again taking aryloxy allylic enol ether **208** and *N*-boc glycine **184**, the coupling was successful and delivered clean material (Scheme 73). After several attempts it was determined that two equivalents of all reagents and only 5 mol% of 4-dimethylaminopyridine (DMAP) were required to ensure consumption of the starting allylic enol ether. Furthermore, the purity of the ester was judged not to warrant additional purification.



Scheme 73: Successful EDCi promoted esterification

2.2.3 *Rearrangement attempts*

With allylic amino ester **198** in hand investigation of the rearrangement was pursued. Traditional Ireland-Claisen rearrangements utilize a strong non-nucleophilic base to generate an enolate with subsquent silylation using a silylating agent, such as trimethylsilyl chloride (TMSCl). Kazmaier's protocol, substitutes the silylating agent for a chelating metal. The formation of the enolate and a secondary anion in the presence of a chelating metal creates a chelated transition state. Thus high levels of metal chelate geometry selectivity can be achieved due to the fixed transition state (Figure 27).

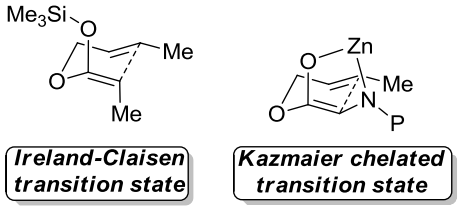
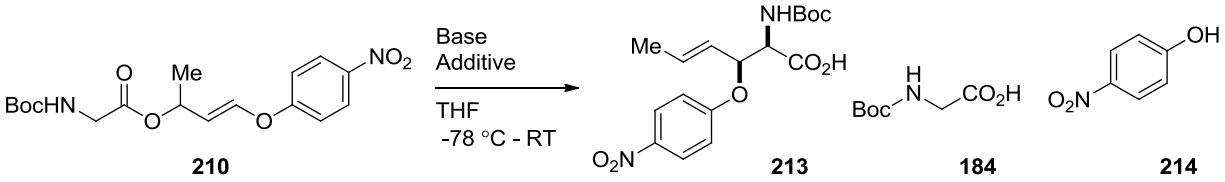


Figure 27: Comparison of transition states

Due to high levels of diastereoselectivity observed by Kazmaier, it was decided to employ the metal chelated Ireland-Claisen rearrangement concept within our rearrangement (Table 3).

Table 3: Rearrangement optimization



210 **213** **184** **214**

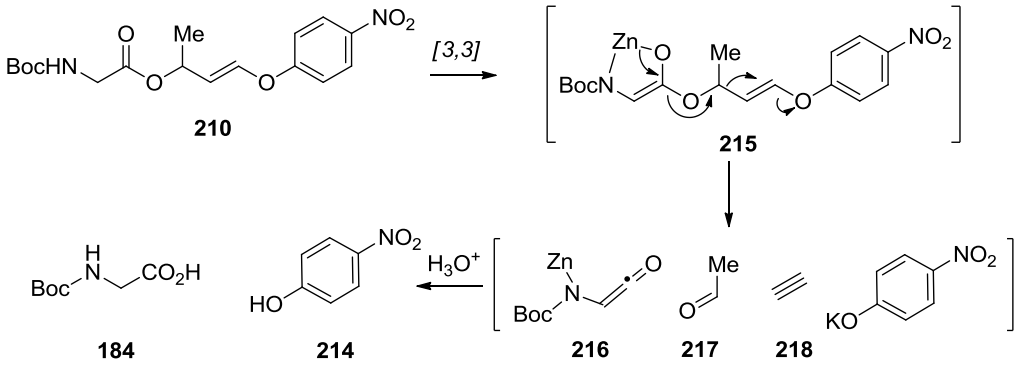
Entry	Base	Equiv.	Additive	Equiv.	Yield 213 (%)	Major Product
1[a]	KHMDS[c]	2.5	$ZnCl_2$	1.1	0	-
2[b]	KHMDS[c]	2.5	$ZnCl_2$	1.1	3	**184 & 214**
3[a]	KHMDS[c]	1.1	$ZnCl_2$[d]	1.1	0	**184 & 214**
4[a]	LiHMDS[c]	3	$ZnCl_2$[d]	3	0	**210**
5[a]	LDA	3	$ZnCl_2$	3	0	**210**
6[a]	KHMDS[c]	1.1	TMSCl	1.1	0	**210**
7[a]	KHMDS[c]	2	TMSCl	2	0	**184 & 214**
8[a]	KHMDS[c]	4	TMSCl	4	0	**184 & 214**

[a] 1M HCl quench used. [b] Methanol quench used. [c] 1M solution in THF. [d] Solution of zinc chloride (1M in ether).

Initial investigation examined the use of Kazmaier's reported protocol (Entry 1).[2] Promisingly, TLC analysis showed the formation of new compounds, with spots more polar than the starting allylic amino ester. After complete consumption of the allylic amino ester, the reaction was worked up using an acidic aqueous procedure as reported by Kazmaier. None of the desired product was isolated from the aqueous wash, however, this was deemed a positive result, due to the high solubility of amino acids in aqueous environments. Repetition of the protocol (Entry 2) ensued, changing the workup procedure. The use of methanol as a protic quench yielded 3% of the rearranged product **213** amongst an intractable mixture of *p*-nitrophenol **214** and *N*-Bocglycine **184**. Significant quantities of insoluble zinc dichloride was present throughout the reaction, therefore suggesting incomplete formation of the zinc chelate, resulting in decomposition to the allylic amino ester's constituent moieties. To help resolve incomplete dissolution of zinc dichloride, an ethereal solution of zinc dichloride was trialed along with a reduction in the equivalents of base used (Entry 3). Due to a reduction in base, incomplete consumption of allylic amino ester **210** was observed. Once again, none of the desired product **213** was isolated, however significant quantities of **214** was obtained from the reaction mixture. Other non-nucleophilic bases

LiHMDS and LDA (Entries 4 & 5) were also investigated. In both cases, quantitative return of the starting allylic amino ester **213** was observed, indicating that under these conditions, neither of these bases were appropriate in promoting the rearrangement. Kazmaier had also observed that TMSCl successfully promotes the rearrangement of a dianionic substrate, however with a reduction in diastereoselectivity. Switching our additive to TMSCl (Entry 6) only a quantitative return of **213** was observed. Increasing the equivalents of base and the additive used (Entries 7 & 8) also lead to decomposition products **184** and **214**.

The formation of **214** is thought to occur *via* a ketene pathway (Scheme 74). Enolisation of **210** and trapping as zinc enolate forms species **215**. Decomposition of **215** leads to the formation of ketene **216**, acetaldehyde **217**, acetylene **218** and *p*-nitrophenoxide. With a sufficiently low pKa, *p*-nitrophenol would act as a suitable leaving group. Upon protic workup, hydrolysis reforms the parent amino acid **184** and *p*-nitrophenol **214**, whilst volatile **217** and **218** are loss. One observation to support this theory is the strong yellow colour observed during the attempted rearrangements which can be attributed to the formation of *p*-nitrophenoxide.



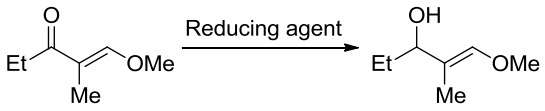
Scheme 74: Possible route for the formation of *p*-nitrophenol 214 and *N*-Bocglycine 184

Due to the decomposition of the allylic amino ester under these conditions and/or the ability of *p*-nitrophenoxide to act as a leaving group, it was deemed necessary to re-evaluate our allylic amino ester and return to investigating the synthesis of alkoxy allylic alcohol.

2.2.4 *Alkoxy Substrate Synthesis*

The reduction of 3-alkoxy α,β-unsaturated ketones was deemed another feasible route into the required alkoxy allylic alcohols. Taking (1*E*)-1-methoxy-2-methyl-1-penten-3-one **219**, several protocols for the reduction of this α,β-unsaturated ketone were investigated (Table 4).

Table 4: Reduction of (1*E*)-1-methoxy-2-methyl-1-penten-3-one, 219



219 **220**

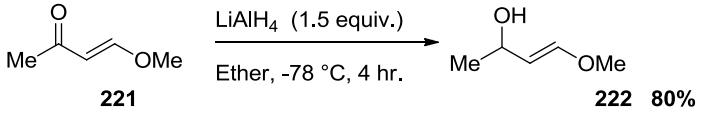
Entry	Reducing Agent	Equiv.	Solvent	Yield (%)
1[a]	DIBAL-H	2.5	Et_2O	0
2[a]	DIBAL-H	5	Et_2O	0
3[a]	DIBAL-H	2.5	Neat	25
4[a]	DIBAL-H	2.5	Hex	27
5	$LiAlH_4$	2	Et_2O	41
6	$LiAlH_4$	4	Et_2O	45
7	$LiAlH_4$	6	Et_2O	60

[a] DIBAL-H (1M in Hexane)

The use of diisobutyl aluminium hydride (DIBAL-H) in ether as the reductant (Entry 1) failed to form the reduced product **220** with only the starting vinylogous methoxy ketone **219** being recovered, even with increased equivalents of DIBAL-H (Entry 2). Successful reduction utilizing hexane as solvent or a neat solution of DIBAL-H lead to successful reduction (Entries 3 & 4), however these reactions were low yielding and purification to remove excess aluminium salts was difficult. Switching hydride source to lithium aluminium hydride (Entry 5) saw an immediate improvement with the removal of aluminium salts made easier and a higher yield obtained, however complete consumption of the starting vinylogous ketone was never obtained when using two equivalents of hydride. Using more equivalents (Entries 6 & 7) further increased consumption of the starting vinylogous ketone and also the yield of the allylic enol ether. Utilizing a large excess of the hydride source had its inherent problems with purification to remove the aluminium salts becoming more difficult, and as such reproducibility of this reduction was very limited. Along with this, the stability of the

product was poor, decomposing rapidly even when cold storage at -18 °C was employed.

Another 1,2-hydride reduction was attempted, this time on the simpler *trans*-4-methoxy-3-buten-2-one **221**. Utilizing lithium aluminium hydride in ether, α,β-unsaturated ketone **221** was successfully reduced to (*E*)-4-methoxybut-3-en-2-ol **222** in 80% yield, and was obtained in sufficient purity to warrant no further purification (Scheme 75).

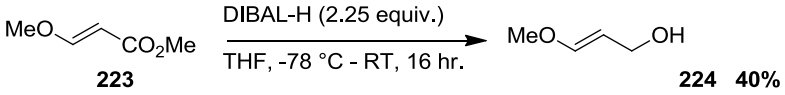


221 **222** **80%**

Scheme 75: Reduction of 221 to 222

Taking both allylic enol ethers **220** & **222**, esterification using the optimised conditions with *N*-Boc glycine did not yield any of the required allylic amino ester.

Several groups had reported the synthesis of primary allylic enol ether (*E*)-3-(methoxy)prop-2-enol **223** from a DIBAL-H mediated reduction of methyl *trans*-3-methoxyacrylate **224** (Scheme 76).[1,124-125]

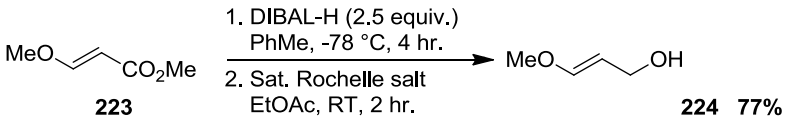


223 **224** **40%**

Scheme 76: Pfaltz conditions for the reduction of 223

Following the protocol described by Pfaltz *et al*. initial results showed that the formation of the correct product was achieved, however several side products were present and complete consumption of the starting alkoxyacrylate could not be obtained under these conditions. Purification of these sensitive products was even more challenging than the previous two alkoxy allylic alcohols synthesized. Careful consideration was required when assaying the product, since the relative acidity of $CDCl_3$ was sufficient to promote the decomposition of the product to acrolein and methanol, therefore it was vital to switch to a non-protic deuterated solvent such as DMSO or acetone. Optimization of this protocol was required to obtain an appropriate quantity suitable for our synthesis. Increasing the equivalents of DIBAL-H to 2.5 and

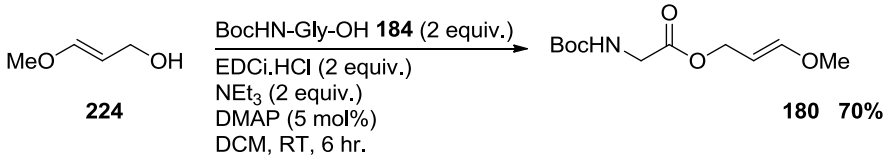
changing the solvent to toluene afforded the correct product, with complete consumption of starting material, however no increase in yield was seen. Importantly, a slow syringe pump addition of DIBAL-H was also required, at a rate of 1 mL/min to help prevent the large exotherms being produced upon the mixing of reagents. Using these improved conditions, the quenching and work-up procedures were next investigated. Pfaltz had used a hydrolysis work-up procedure, leading to the formation of a thick slurry of aluminium salts. Filtration of these salts was slow and with the high viscosity of the salts the possibility arose of incomplete product isolation hence a low mass return from the reaction. Quenching at -78 °C with methanol produced a precipitate which was easier to filter and less aluminum salts were present in the final product. Careful purification by Kugelrohr bulb-to-bulb distillation yielded the product in an improved yield of 64%. Several groups have reported that the addition of saturated Rochelle salt solutions to their reduction mixture quenches the reaction whilst avoiding the formation of the notoriously difficult to remove aluminium salts.[126] When used in our system this resulted in an extremely difficult separation with none of the desired product isolated. Cossey e*t al*. reported the use of an inverse Rochelle salt quench, where the reduction mixture was added into a saturated solution of Rochelle salt, in their synthesis of allylic enol ethers.[127] Following this workup protocol the required alkoxy allylic enol ether was obtained in a desirable 77% yield and even more significant, without the need for further purification (Scheme 77).



223 **224** **77%**

Scheme 77: Optimized conditions for the reduction of 223

With the required alkoxy allylic enol ether **224** in hand, the required allylic amino ester was synthesized using carbodiimide coupling to afford the required substrate in a 70% yield (Scheme 78).



224 **180** **70%**

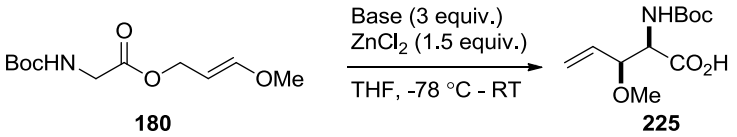
Scheme 78: Synthesis of allylic amino ester 180

Once again, the sensitivity of this substrate was clear to see. Should the esterification require purification, flash chromatography was inappropriate, causing the allylic amino ester to degrade. Instead, resubjecting to further aqueous washes was usually sufficient to afford **180** in sufficient purity to proceed. Furthermore, cold storage was also required to also prevent short term decomposition.

2.2.5 *Alkoxy substrate rearrangement attempts*

With substrate **180** in hand, the rearrangement to form β-alkoxy α-amino acids was investigated, initially utilizing the protocol developed by Kazmaier *et al.* (Table 5).[2]

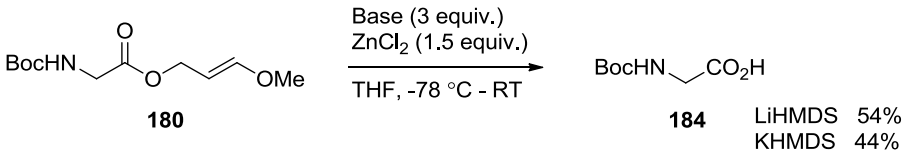
Table 5: Attempted rearrangement of 180



Entry	Base[a]	Additive[b]	Yield (%)	Major Product
1	KHMDS	$ZnCl_2$	0	BocHN-Gly-OH
2	LiHMDS	$ZnCl_2$	0	BocHN-Gly-OH

[a] 1M solution in THF. [b] 1M solution in Et_2O.

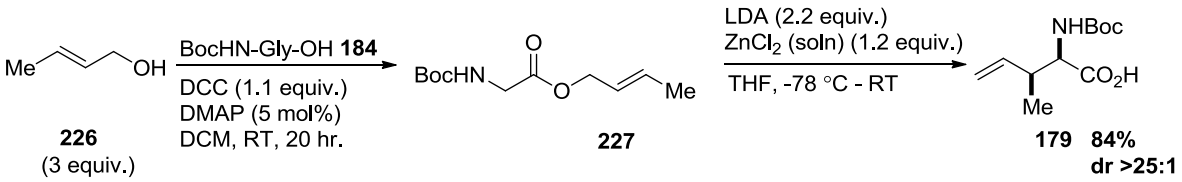
The use of either KHMDS or LiHMDS none of the desired product was observed. Instead both promoted a decomposition pathway back to the parent amino acid, *N*-Boc glycine, consistent with that reported for the aryloxy allylic amino esters (Scheme 79).



Scheme 79: Formation of *N*-Boc glycine 184 upon attempted rearrangement of 180

Due to the lack of success of our desired rearrangement, a substrate reported by Kazmaier was prepared *via* a *N*,*N*'-dicyclohexylcarbodiimide (DCC) mediated coupling of crotyl alcohol **226** and *N*-Boc glycine **184** and the rearrangement was investigated. Subjecting allylic amino ester **227** to Kazmaier's protocol yielded a successful

rearrangement to amino 3-methylpent-4-enoic acid **179** in good yield and diastereoselectivity (Scheme 80). This result is in line with the reported data by Kazmaier and prompted us to consider the suitability of our substrate in these rearrangements.



Scheme 80: Repetition of a reported Kazmaier substrate

Ireland reported that the addition of an enol ether leads to a stereoelectronic effect, affecting the relative stability of the chairlike transition.[1] Hence donation of the ethereal oxygen's lone pair of electrons leads to increased dipolar character in the transition state. Significantly this may cause a substantial increase in the rate of bond cleavage compared to bond formation. In our system, the degree of electron donation seems to be to such a high level that bond cleavage is observed instead of any sigmatropic rearrangement occurring, therefore leading to the degradation products observed. In addition to this, our system includes an electron rich nitrogen atom. Donation of the anionic charge build up on the nitrogen into the π-system of the enolate and then subsequently into the C-Oσ∗ orbital can further increase the dipolar character of the transition state, and therefore further increase the rate of bond cleavage. Thus it can be considered that the formed intermediate is too high in energy, therefore becoming inherently unstable leading to decomposition of the allylic ester enolate system.

The formation of this parent amino acid can be hypothesized to occur due to the presence of the dianionic nature of the intermediate enolate (Figure 28). Upon formation of the enolate of the allylic ester, the central C-Oσ□* orbital is overlapped by two highly electron rich π-systems allowing a significant level of electron density to be donated into this C-Oσ* orbital.

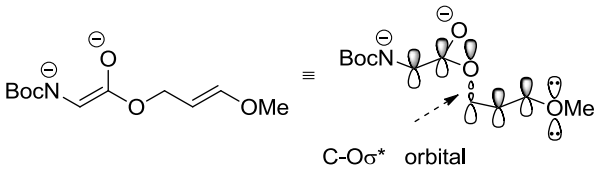


Figure 28: Possible enolate instability

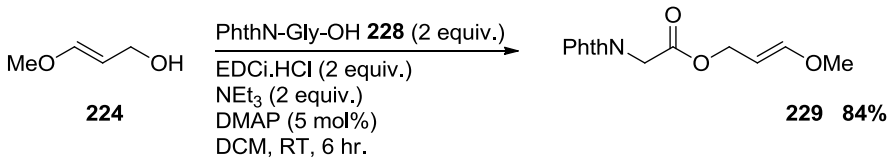
Should the instability of the allylic enolate be caused by the anionic nitrogen centre, then substituting the acidic *N*-H proton should allow for successful rearrangement. The major drawback and item to note is that the use of Kazmaier's protocol would have to be swapped for more traditional Ireland-Claisen rearrangement protocols.

2.3 SECOND-GENERATION IRELAND-CLAISEN SUBSTRATE

After observing a significant increase in the stability of the aryl allylic enol ether by reducing the amount of electron pair donation, a similar setup was deemed suitable to prevent nitrogen lone pair donation. Taking this into account we decided to investigate the use of a phthalimde (Phth) protecting group. Protection of the amino nitrogen as an imide not only removes the acidic *N*-H proton and prevents the build up of an anionic charge, but should significantly reduce the ability of the nitrogen to donate the lone pair of electrons through the enolate π-system in to the C-Oσ∗. This in turn should hopefully reduce the rate of bond cleavage and the decomposition pathways.

2.3.1 *Forward synthesis*

Taking alkoxy allylic enol ether **224** and *N*-phthaloyl glycine **228,** the required allylic amino ester was synthesized using carbodiimide coupling to afford the required substrate in 84% yield (Scheme 81).

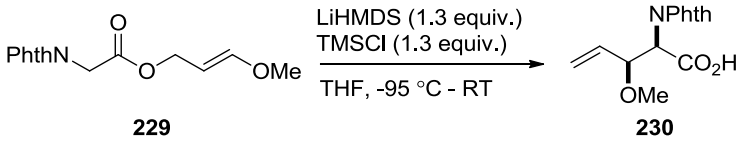


Scheme 81: Allylic amino ester 229 synthesis

The stability of the allylic amino ester had been significantly increased by the addition of the phthalimde functionality. The substrate formed was a considerably easier to handle solid, and little degradation was seen with cold storage over several months.

With the second generation allylic amino ester **229** in hand, we next turned our attention to the rearrangement. An initial attempt at rearrangement showed complete consumption of the starting allylic amino ester by TLC analysis (Scheme 82). ^{1}H NMR analysis of the crude reaction mixture confirmed the consumption of allylic amino ester

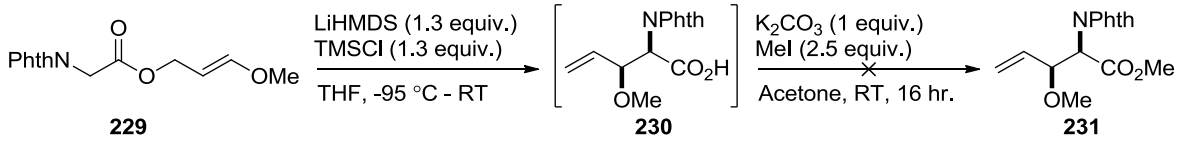
229 along wtith the formation of a new compound consistent with the product obtained after rearrangement of Kazmaier's allylic amino ester **227**. Purification of the crude amino acid, proved difficult and therefore it was decided to derivatize the crude amino acid to its methyl ester,which significantly increased the stability of the product and allowed for chromatographic purification.



229 **230**

Scheme 82: Successful rearrangement of 229 to 230

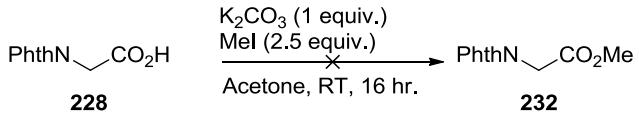
After complete consumption of the starting allylic amino ester by TLC was observed, the reaction was quenched using 1M HCl solution and extracted with DCM. Upon isolation the residue was subjected to a methylation using potassium carbonate and methyl iodide (Scheme 83). There are several reports in the literature on the synthesis of amino methoxy esters from amino acids. Valle *et al.* used a protocol utilizing methyl iodide in the presence of potassium carbonate in their synthesis of Lucentamycin A.[128] None of the expected amino ester **231** was isolated. It was observed that a vast number of different phthalimide signals in the crude ^{1}H NMR spectra. None of the required amino ester was recovered possibly due to degradation of the putative potassium carboxylate intermediate.



229 **230** **231**

Scheme 83: Rearrangement of 218 and attempted protection as the methyl ester

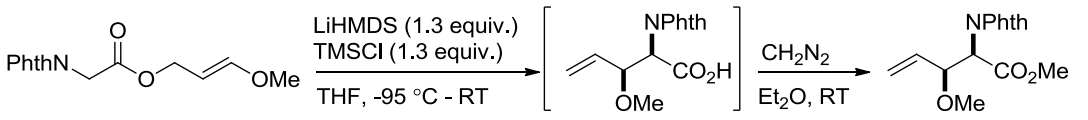
A test reaction, subjecting phthaloyl glycine **228** to a methylation using the same conditions, confirmed this, since once more a large number of different phthalimide signals were present in the crude ^{1}H NMR spectra, and none of the desired amino ester **232** was isolated (Scheme 84).



228 232

Scheme 84: Attempted protection of *N*-phthaloyl glycine as the methyl ester

Next we turned our attention to a significantly more rapid protocol utilizing diazomethane as reported by Molanski *et al.* in the synthesis of sagittamides A and B.[129] As observed before, complete consumption of the starting allylic amino ester was observed. The reaction was quenched using a 1M HCl/brine (1:1) solution and extracted with ethyl acetate and dichloromethane, then concentrated *in vacuo*. The crude residue treated with a freshly prepared ethereal solution of diazomethane to afford methyl ester **231.** After purification *via* flash chromatography compound **231** was isolated in a 21% yield (Scheme 85).

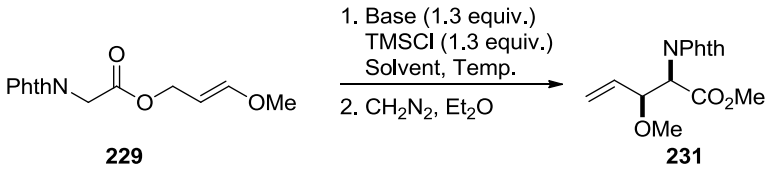


229 230 231 21%

Scheme 85: Successful rearrangement of 229 and protection forming 231

Although low yielding, the desired product was isolated cleanly and therefore all subsequent rearrangements, were treated with diazomethane to aid purification and isolation. However, do to the low yield obtained, an optimization study was initiated (Table 6).

Table 6: Rearrangement optimization



229 **231**

Entry	Base	Solvent	Temperature (°C)	Yield (%)	dr
1	LiHMDS	THF	-78	0[a]	-
2	NaHMDS	THF	-78	0[a]	-
3	KHMDS	THF	-78	0[a]	-
4	LiHMDS	THF	-95	74	11:1
5	LiHMDS	Et_2O	-95	65	9:1
6	LiHMDS	PhMe	-95	0[a]	-
7	NaHMDS	THF	-95	45	7:1
8	KHMDS	THF	-95	34	6:1
9	LDA	THF	-95	0[a]	-
10[b]	LiHMDS	THF	-95	0[a]	-

[a] Intractable reaction mixture. [b] TIPSOTf used as a silylation additive.

Due to the initial success where by obtaining rearranged material was obtained using 1.3 equivalents of both base and silylating agent, it was decided to keep the equivalents used at this level. After considerable investigation it was determined that for efficient rearrangement to occur, LiHMDS was to be added over 15 minutes *via* syringe pump to a solution of allylic amino ester **229** and TMSCl in THF at -95 °C before warming to 0 °C (Entry 4). When the reaction was initiated at higher temperatures (-78 °C, Entries 1, 2 & 3) or when non-ethereal solvents such as toluene were used (Entry 6), the reaction yielded an intractable mixture of products. Crude ^{1}H NMR analysis observed a mixture of the desired rearranged product along with elimination products, α-silylation products and also unconverted starting allylic amino ester. The use of Na- (Entry 7) or KHMDS (Entry 8) at -95 °C, leads to successful rearrangement, however a significant drop in reaction quality was observed, in terms of both yield and diastereoselectivity. The use of another Li-amide base (LDA, Entry 9) or a different silylating agent (TIPSOTf, Entry 10) also lead to an intractable reaction mixture.

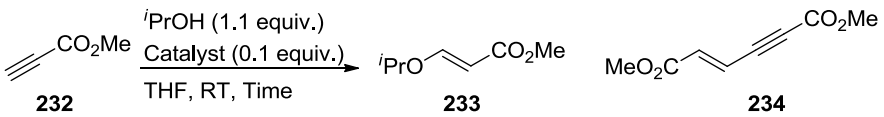
2.4 *N*-PHTHALIMIDE SUBSTRATES

With the optimal reaction conditions identified, the generality of the rearrangement was investigated. A range of ethereal substrates were synthesized and investigated.

2.4.1 *Substrate Synthesis*

With methyl *trans*-3-methoxyacrylate being the only commercially available vinylogous ester, a route to the synthesis of a range of analogues was investigated to keep our allylic amino ester synthesis consistent. Several reagents have been reported to catalyze the 1,4-addition of oxygen nucleophiles to activated acetylenes.[121,130-131] With a selection investigated for the addition of isopropanol to methyl propiolate **232** (Table 7).

Table 7: 1,4-Addition optimization



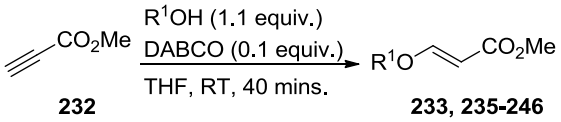
Entry	Catalyst	Time (hr)	Yield 233 (%)
1	NMM	4	65
2	P(^{n}Bu)$_3$	24	74
3	DABCO	0.5	70

N-Methylmorpholine (NMM, Entry 1) afforded vinylogous ester **233** in 65% yield, however, 20% of homo coupled product **234** was also obtained. The use of tri^{n}butylphosphine (Entry 2), afforded **233** in 74% yield, however, required a significantly longer reaction time. This extended reaction time was required due to the necessity of opening the reaction to the air for 23 hours to oxidize the catalyst to aid removal. Filtration of the phosphine oxide was followed by distillation to remove any further traces. Finally, a DABCO mediated reaction (Entry 3), rapidly delivered the desired product in good yield. With significantly less of homo coupled product **234** being obtained (<10%) with purification by flash chromatography sufficient to afford pure **233** in 70% yield. In all three trials only the (*E*)-isomer was obtained.

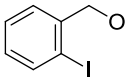
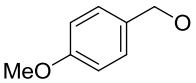
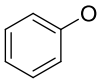
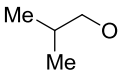
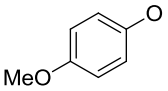
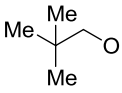
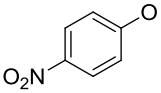
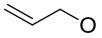
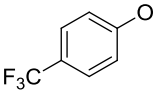
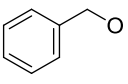
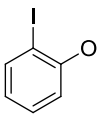
Although none of homo coupled product **234** was observed when using tri^{n}butylphosphine as the catalyst, the long reaction times and the need for purification by distillation, would mean that a rapid synthesis of several different analogues *via* this method would be time consuming. Therefore the use of the DABCO catalysed protocol would be better employed.

Having optimized the DABCO catalyzed 1,4-addition, several different alcohols were reacted with methyl propiolate to afford vinylogous esters **233, 235 - 246** (Table 8).

Table 8: DABCO catalyzed 1,4-addition into methyl propiolate



232 **233, 235-246**

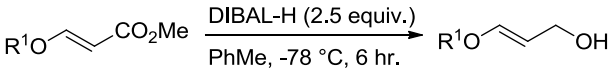
Entry	OR[1]	Product	Yield (%)	Entry	OR[1]	Product	Yield (%)
1	O^{i}Pr	**233**	70	**8**		**240**	91
2	OEt	**235**	88	**9**		**241**	78
3	O^{t}Bu	-	0	**10**		**242**	98
4		**236**	86	**11**		**243**	82
5		**237**	92	**12**		**244**	98
6		**238**	85	**13**		**245**	93
7		**239**	86	**14**		**246**	93

All alcohols successfully reacted with methyl propiolate to form the desired vinylogous ester in good to excellent yields (70 – 98%) with the exception of one. *tert*-Butanol (Entry 3), was the only alcohol where vinylogous carbonate formation was not

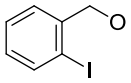
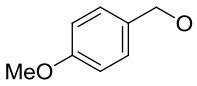
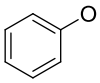
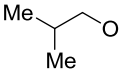
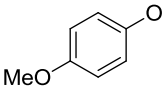
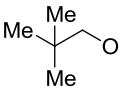
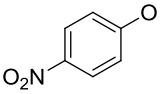
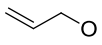
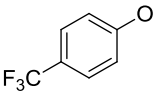
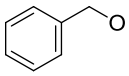
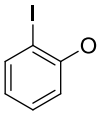
observed, and was most likely to be caused by the low nucleophilicity of tertiary alcohols. Only one example of a secondary alcohol used to form a secondary ethereal fragment was examined.

Having previously optimized the DIBAL-H reduction, all vinylogous esters were successfully reduced to the required allylic enol ethers with these optimized conditions (Table 9).

Table 9: Vinylogous ester reductions



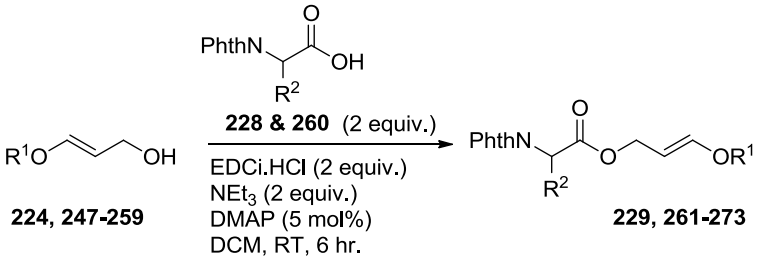
233, 235-246 **224, 247-259**

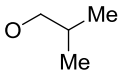
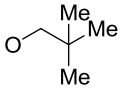
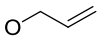
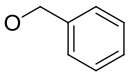
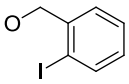
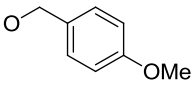
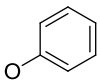
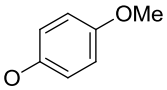
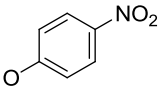
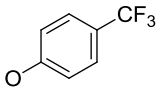
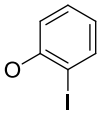
Entry	OR^1	Product	Yield (%)	Entry	OR^1	Product	Yield (%)
1	OMe	**224**	77	**8**		**253**	91
2	OEt	**247**	88	**9**		**254**	78
3	O^{i}Pr	**248**	70	**10**		**255**	98
4		**249**	86	**11**		**256**	82
5		**250**	92	**12**		**257**	89
6		**251**	85	**13**		**258**	93
7		**252**	86	**14**		**259**	93

All of the vinylogous esters were successfully reduced to the allylic enol ether in good yield (70 – 98%), none of which required further purification. All allylic enol ethers were extremely sensitive to a wide range of conditions and suitable precautions had to be taken to prevent decomposition.

Using the optimized carbodiimide promoted protocol the desired allylic amino esters were synthesized from either *N*-Phthaloyl glycine or *N*-Phthaloyl alanine (Table 10).

Table 10: Allylic amino ester synthesis



Entry	OR^1	R^2	Product	Yield (%)
1	OMe	H	**229**	84
2	OEt	H	**261**	78
3	O^{i}Pr	H	-	0
4		H	**262**	61
5		H	**263**	76
6		H	**264**	71
7		H	**265**	74
8		H	**266**	70
9		H	**267**	56
10		H	**268**	82
11		H	**269**	77
12		H	**270**	69
13		H	**271**	73
14		H	**272**	73
15	OMe	Me	**273**	95

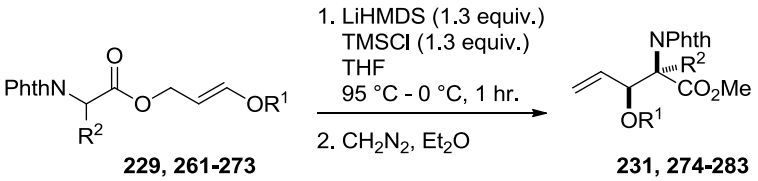
All of the allylic enol ethers coupled in good yield (56 – 91%) except for one, (Entry 3, R = isopropyl). In this case only an intractable mixture of products was obtained. Due to

the sensitivity of these products, purification or isolation of the desired allylic amino ester was not achievable. Although this protocol seems to be restricted to primary ethereal systems, importantly, the amino acid coupling partner is not restricted to glycine. Entry 15 shows the successful coupling of phthaloyl proctected alanine in excellent yield.

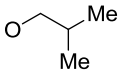
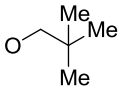
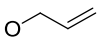
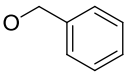
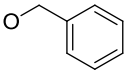
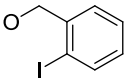
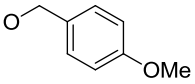
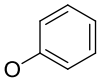
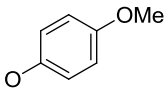
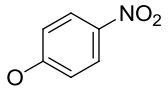
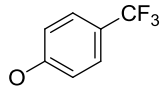
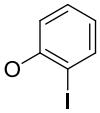
2.4.2 *Substrate rearrangement*

With a wide range of allylic amino esters in hand, the scope of the rearrangement could be investigated utilizing the optimized rearrangement protocol (Table 11).

Table 11: Scope of enol ether in rearrangement

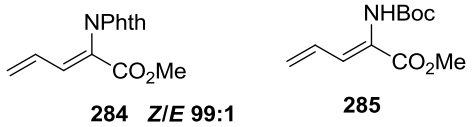


229, 261-273 **231, 274-283**

Entry	Allylic amino ester	OR^1	R^2	Product	Yield (%)[a]	dr[b] (*syn*:*anti*)
1[c]	**229**	OMe	H	**231**	74	11:1
2[c]	**261**	OEt	H	**274**	79	9:1
3[c]	**262**		H	**275**	64	18:1
4[c]	**263**		H	**276**	78	13:1
5[c]	**264**		H	**277**	70	10:1
6[c]	**265**		H	**278**	70	10:1
7[d]	**265**		H	**278**	64	2:1
8[c]	**266**		H	**279**	50	14:1
9[c]	**267**		H	**280**	63	8:1
10[c]	**268**		H	**281**	81	14:1
11[c]	**269**		H	-	0[e]	-
12[c]	**270**		H	-	0[f]	-
13[c]	**271**		H	-	0[f]	-
14[c]	**272**		H	**282**	50	>25:1
15[c]	**273**	OMe	Me	**283**	71	24:1

[a] Isolated yield. [b] Diastereomeric ratio measured by ^{1}H NMR analysis of crude reaction mixtures.
[c] LiHMDS solution added over 15 minutes by syringe pump. [d] LiHMDS solution added over 1 minute by hand. [e] Intractable mixture. [f] Starting allylic amino ester recovered in >95%.

The rearrangement is seen to be general, offering yields of 50 - 81% and diastereoselectivites of ≥8:1. A large range of *O*-functionality has been investigated and is tolerated, starting with simple alkyl substrates (Entries 1 & 2). Other alkyl groups such as isobutyl (Entry 3) and neopentyl (Entry 4) also successfully rearrange. Access to similar compounds containing isobutyl or neopentyl alkylated oxygens would be extremely difficult using more traditional alkylating methodologies, due to the requirement of extremely poor alkyating agents. A wide range of hydroxyl protecting groups (Entries 5, 6 & 9) were also tolerated. Importantly, substrates containing further synthetic handles (Entries 5, 8 & 14) also rearrange and provide excellent diastereoselectivity. Phenoxy derived amino allylic ester afford interesting chemoselectivity. Substrates containing electron-donating groups (Entry 11) saw complete consumption of the allylic amino ester, however furnishing a complex reaction mixture with the only identifiable component being diene **284** (Figure 29). It is believed diene **284** is resultant from successful rearrangement followed by a facile $E1_{CB}$ elimination of the β-phenoxy α-amino acid product. Confirmation of this was achieved by comparison to an independently prepared diene **284**. Alkene geometry was confirmed by comparison of experimental data reported by Takahashi for diene **285** (Figure 29).[132] Later confirmation was also obtained by nuclear overhauser effect spectroscopy (NOeSY).



284 ***Z/E*** **99:1** **285**

Figure 29: Diene 284 and diene 285

In contrast, electron-withdrawing substituents (Entries 12 & 13) inhibit the rearrangement. They were observed not to undergo rearrangement; instead complete recovery of the starting allylic amino ester was obtained from the reaction mixture. Substrates **268** and **272** (Entries 10 & 14) have no effect upon the rearrangement and proceeded to the rearranged products in high diastereoselectivity. Also satisfying was the rearrangement of an allylic amino ester derived form *rac*-alanine (Entry 15) with high levels of *syn*-selectivity once more being observed. More importantly this result now opens up a general diastereoselective route into synthesizing serine/alanine adducts

or further α,α-substituted hybrid amino acid fragments utilizing this methodology. The synthesis of these amino acid residues are important due to the resemblence seen in several natural products such as sphingofungin F **286**.

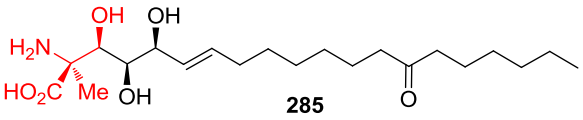
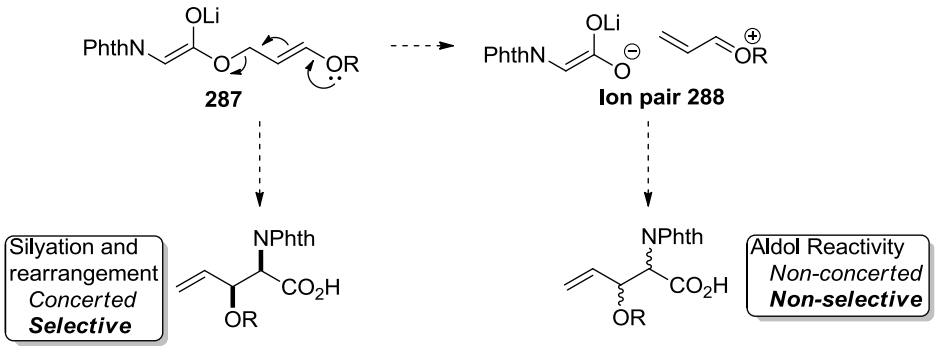


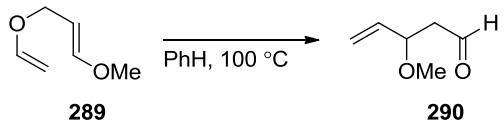
Figure 30: Sphingofungin F 286

The diastereoselectivity of this rearrangement appears to be particularly sensitive to initial rearrangement conditions. This is clearly seen for the benzyloxy substrate **265** (Entry 6) with a 10:1 diastereoselectivity ratio observed when base addition was completed *via* syringe pump over 15 minutes. A much faster addition of base over 1 minute by hand (Entry 7), led to a dramatic reduction in diastereoselectivity with an observed diastereoselectivity of 2:1. This observation could be consistent with a non-concerted mechanism taking place. A possible scenario is the rate enhancement in the breaking of the C-Oσ bond of intermediate enolate **287** into ion pair **288**. Recombination of the lithium glycinate nucleophile with the acrolein oxonium electrophile then takes place *via* a non-concerted, non-selective aldol type pathway (Scheme 86).



Scheme 86: Possible selective or non-selective reactions of enolate 287

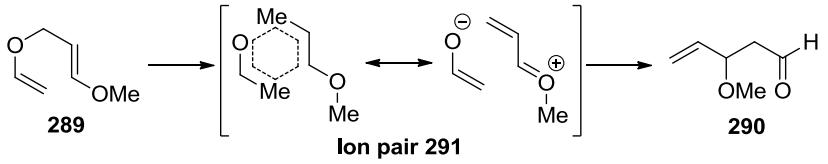
Curran *et al.* have described polarized transition states and observed rate enhancement of the rearrangement of methoxy-substituted allyl vinyl ethers in the Claisen rearrangement (Scheme 87).[133]



289 **290**

Scheme 87: Curran's Claisen rearrangement of methoxyallyl vinyl ether 289

Kinetic studies have shown that methoxyallyl vinyl ether **289** rearranged more rapidly than unsubstituted allylvinyl ether (k_{rel} = 9.5 *cf.* 1.0). Switching to a hydrogen bonding solvent, in this case methanol, further enhances the rate of rearrangement (k_{rel} = 68 *cf.* 1.7). The addition of the methoxy enol ether leads to rate enhancement due to two effects: enol ether resonance and vinylogous anomeric stabilization. Along with this an increase in dipolar character of the transition state is attributed to the increase in rate of reaction. Partial delocalization of a non-bonded pair of electrons from the enol ethereal oxygen leads to the formation of an enolate and oxonium ion pair, which stabilize the transition state to a greater extent than the ground state. Therefore, these enhanced rates might suggest that the rearrangement is proceeding through a two step non-concerted mechanism with ion pair **291**, as the reactive intermediate (Scheme 88). It is thought that the effects seen in this report mirror the effect observed in our rearrangement and therefore low levels of diastereoselectivity observed upon rapid base addition can be attributed to a similar effect.



289 **Ion pair 291** **290**

Scheme 88: Curran's Claisen rearrangement of methoxyallyl vinyl ether 289 throug ion pair 291

The relative stereochemistry of the rearrangement was confirmed through X-ray crystallographic analysis of cesium carboxylate **292** (Figure 31). The observed diastereoselectivity suggests the reaction proceeds *via* the intermediate (*Z*)-SKA, through chairlike transition state **293** affording the *syn*-selective product.

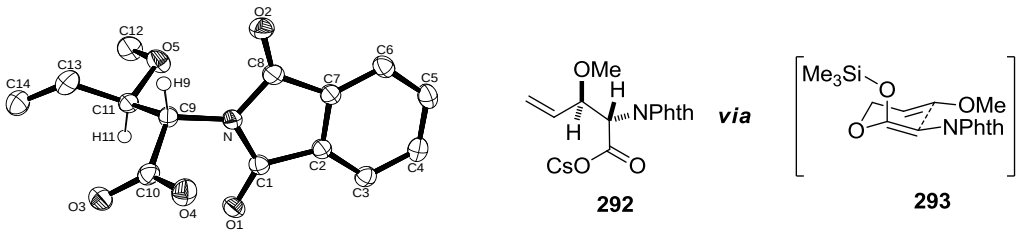


Figure 31: ORTEP plot of cesium carboxylate 292 (ellipsoids shown at 30% probability) and chair transition state 293

2.5 CONCLUSIONS

We have developed a new Ireland-Claisen approach to β-hydroxy α-amino acids. From initially looking at metal chelated enolates, where none of the desired products were obtained, switching to a more traditional Ireland-Claisen type protocol, allowed for *syn*-selective rearrangement. Although the rearrangement is particularly sensitive to a wide range of variables such as initiation temperature and base addition rate, a wide range of enol ethers can be tolerated to rearrange to the desired β-hydroxy α-amino acids in good yields and diastereoselectives. However the scope of the rearrangement is limited. Only allylic enol ethers containing primary or phenoxy based ethereal groups can be successfully coupled to form the required allylic amino ester. Can changing the *N*-protecting group on the amino acid influence the carbodiimide promoted coupling and allow for the synthesis of secondary enol ether substrates? And also can greater selectivity, or possible to achieve complete diastereocontrol?

CHAPTER 3 ALTERNATIVE NITROGEN PROTECTION

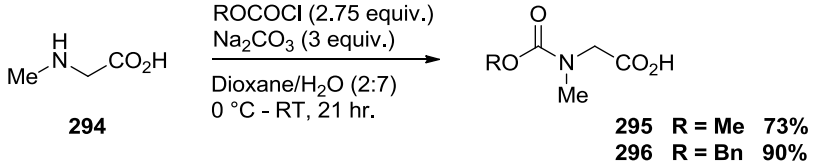
3.1 AMINO ACID INVESTIGATION

Having obtained proof of principle in the desired rearrangement with *N*-phthaloyl allylic amino esters and assaying the scope of the enol ether, several key factors still required investigation. Although the phthaloyl protecting group was suitable, deprotection could not be achieved. Furthermore, incorporation of other nitrogen functionality could allow for further synthetic elaborations. Finally, the observed diastereoselectivity is good in some instances, however there seems to be considerable room for improvement. Therefore an investigation into the scope of the *N*-protection was initiated.

3.1.1 *Amino acid synthesis*

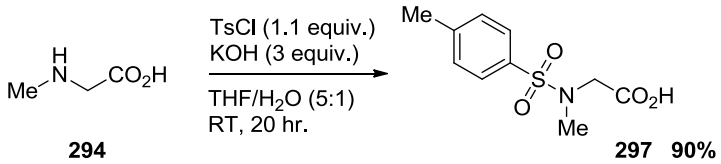
It was observed early on that the electronic nature of the nitrogen protecting groups play a substantial part in stabilizing the enolate formed prior to silylation. Thus, by reducing the electron donating capability should allow for a decrease in lone pair overlap with the enolate π-system allowing for a successful rearrangement to proceed. A broad range of protected glycines that were investigated included several commercially available derivatives, along with several synthesized variants where the electron withdrawing nature of the protecting group is suitable to stabilize the transition state of the rearrangement.

Initial investigation was centred on a range of protected sarcosines. Following the protocol reported by Brimble *et al*. in 2005, sarcosine **294** was subjected to either methyl or benzyl chloroformate in the presence of sodium carbonate to yield the methoxycarbonyl or benzyloxycarbonyl (Cbz) protected sarcosine respectively (Scheme 89).[134]



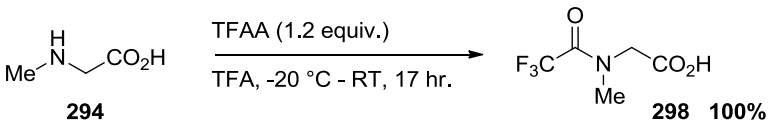
Scheme 89: Synthesis of methoxy and benzyloxy carbamate protected sarcosines

A toluene sulfonamide derivative was synthesized by the addition of tosyl chloride in the presence of potassium hydroxide in good yield as reported by Rossello *et al.* in 2006 (Scheme 90).[135]



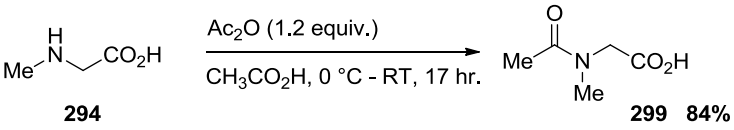
Scheme 90: Tosyl protected sarcosine

The synthesis of a trifluoroacetamide protected sarcosine proved considerably more complex. Several different sets of conditions were trialed until eventually utilizing the procedure described by Weygand. Amino acid **298** was synthesized using trifluoroacetic anhydride in trifluoroacetic acid at -20 °C in quantitative yield. The temperature at which the reaction was performed was vital for the successful synthesis of **298** (Scheme 91).[136]



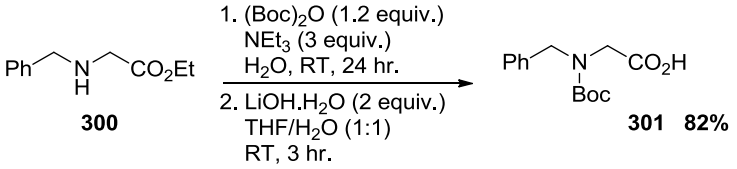
Scheme 91: Trifluroracetimide protected sarcosine

Adapting this procedure, the reduced electron withdrawing acetamide functionality was installed in an 84% yield (Scheme 92).



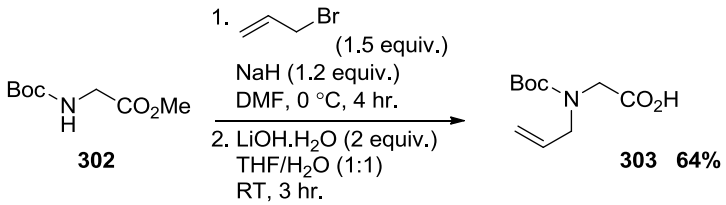
Scheme 92: Actetimide protected sarcosine

With a range of protected sarcosines synthesized, a range of di substituted glycines where both groups can be considered as protecting groups (*i.e.* not a methyl group) were synthesized. In all cases, on of the groups was maintained as a Boc group. Firstly, 2-(benzyl(*tert*-butoxycarbonyl)amino)acetic acid **301**, was synthesized starting from *N*-benzyl glycine ethyl ester **300**. Subjecting **300** to di-*tert*-butyl dicarbonate in the presence of triethylamine followed by saponification utilizing lithium hydroxide afforded **301** in 82% over two steps (Scheme 93).



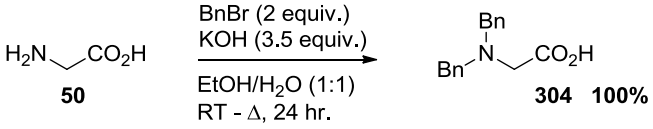
Scheme 93: *N*-Boc, benzyl glycine synthesis

The addition of allyl bromide to *N*-Boc glycine methyl ester **302** in the presence of sodium hydride yielded the allyl protected amino ester. Saponifcation of the methyl ester afforded the desired amino acid **303** in a 64% yield over the two steps (Scheme 94).



Scheme 94: *N*-Boc, allyl glycine synthesis

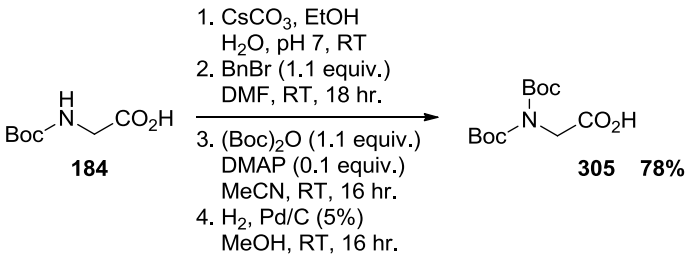
Although two different protecting groups allow for selective deprotection to the secondary amine, inclusion into a natural product synthesis requiring a primary amine would require two deprotections, therefore a selection of di-protected amino acids, with the same protecting groups were also synthesized. Using the protocol reported by Heimgartener, glycine was subjected to benzyl bromide and potassium hydroxide at reflux to afford the desired dibenzyl glycine **304**, in quantitative yield (Scheme 98).[137]



Scheme 98: Dibenyl glycine synthesis

The synthesis of a di-Boc protected glycine as reported by Gunnarson was more in-depth (Scheme 99).[138] Firstly, the cesium carboxylate of *N*-Boc glycine was treated with benzyl bromide, forming the benzyl ester. Taking the benzyl ester in acetonitrile and subjecting to di-*tert*-butyl dicarbonate in the presence of catalytic DMAP yielded the *N*-diboc glycine benzyl ester. This in turn was subjected to hydrogenolysis in the presence of catalytic palladium on carbon to afford the *N*-diboc glycine in a 78% yield for the

four steps. Later the synthesis of **305** was reduced to three steps by utilizing an EDCi coupling between *N*-Boc glycine and benzyl alcohol to form the benzyl ester, again yielding **305** in 78% across the three steps.

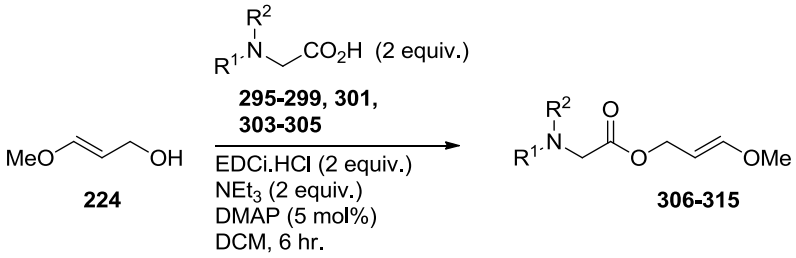


Scheme 99: Diboc glycine synthesis

3.1.2 *Substrate synthesis*

Initially investigation into different nitrogen protecting groups looked at rearrangements utilizing the methoxy allylic enol ether **224**. The required substrates were synthesized *via* a carbodiimide coupling in order to keep our allylic amino ester synthesis constant (Table 12).

Table 12: Methoxy allylic amino esters synthesis utilizing a range of amino acids

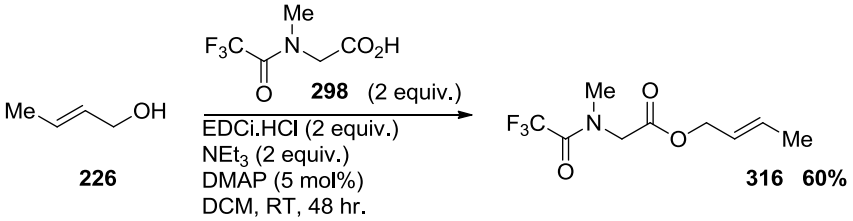


Entry	R^1	R^2	Product	Yield (%)
1	Boc	Me	**306**	77
2	CO_2Me	Me	**307**	87
3	Cbz	Me	**308**	97
4	Ts	Me	**309**	60
5	Ac	Me	**310**	73
6	F_3CCO	Me	**-**	0
7	Boc	Allyl	**311**	60
8	Boc	Bn	**312**	85
9	Me	Me	**-**	0
10	Bn	Bn	**313**	76
11	Boc	Boc	**314**	70
12	*N*-Boc Proline		**315**	65

All products that contain a carbamate protecting group, except for *N*-diboc glycine were obtained as a rotameric mixture. Rotamers are conformational isomers arising from restriction of rotation around a bond.[139] In particular, rotamers are observed upon the ^{1}H NMR timescale and observed as two or more signals. The presence of rotamers can be confirmed by variable temperature (VT) ^{1}H NMR analysis, heating the system, decreases the restriction within this rotation and therefore coalescence of the rotameric peaks being observed. All of our allylic amino esters and other products where rotamers were present were confirmed by the coalescence of these peaks *via* ^{1}H VT NMR.

Successful esterification of **224** with a range of amino acids was achieved, however, changing the *N*-protecting group had no bearing upon the stability of the allylic amino ester as they were still sensitive to purification. Only in two cases was the desired allylic amino ester was not obtained. When using the trifluororacetimide protected sarcosine (Entry 6), TLC analysis showed a successful coupling to the desired substrate.

However, upon workup or before analysis by ^{1}H NMR could be carried out, degradation of the allylic amino ester substrate was observed to occur. To confirm a successful coupling had been achieved, a test coupling of amino acid **298** and with crotyl alcohol **226** was undertaken (Scheme 100).

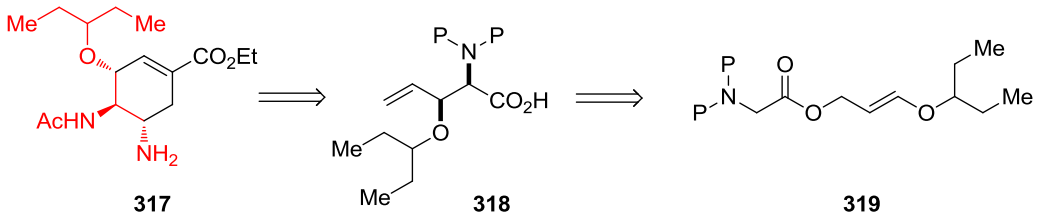


Scheme 100: Successful coupling of 298 with 226

Although a significantly longer reaction time was required, a successful coupling was performed, with comparable TLC analysis to that of the coupling utilizing methoxy allylic enol ether **224**, showing a successful reaction had occurred, however, the allylic amino ester was unstable and degradation occurred before the rearrangement could be investigated. Also *N*-dimethyl glycine (Entry 9) failed to afford the coupled product, with a quantitative return of the parent amino acid being obtained.

Carbamate protected sarcosines (Entries 1, 2 & 3) all coupled successfully in good yield with Cbz protected sarcosine in particular affording the desired allylic amino ester in near quantitative yield. *N*-Tosyl sarcosine (Entry 4) successfully coupled, although at a reduced yield along with the acetamide sarcosine (Entry 5). Both examples of glycine with two different protecting groups (Entries 7 & 8) successfully coupled in good yield. Two amino esters containing the same *N*-protecting group were also successfully synthesized (Entries 10 & 11), whilst finally, a second α-functionalized amino acid in the form of proline was also successfully coupled (Entry 12).

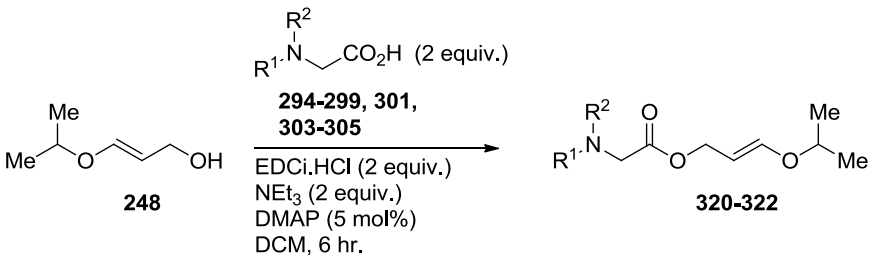
A significant number of important and relevant biologically active molecules contain secondary ethers such as Oseltamivir (Tamiflu) **317**(Scheme 101). Due a significant requirement for stock piles of Oseltamivir, new synthetic routes for the synthesis of **317** have become rife in the literature.[139-141] It was felt that the synthesis of Oseltamivir could be achieved utilizing this methodology.



Scheme 101: Anticipated approach to Oseltamivir 317

To allow for the synthesis of Tamiflu or another target containing a secondary ether using this methodology it would be required to synthesise and rearrange an allylic amino ester containing a secondary ethereal oxygen. All amino acids trailed in Table 12 (*vide supra*) were also subjected to carbodiimide esterification utilizing isopropoxy allylic enol ether **239** (Table 13).

Table 13: Isopropoxy allylic amino esters synthesis utilizing a range of amino acids



Entry	R^1	R^2	Product	Yield (%)
1	Boc	Me	**320**	49
2	CO_2Me	Me	**321**	47
3	Cbz	Me	-	0
4	Ts	Me	-	0
5	Ac	Me	-	0
6	F_3CCO	Me	-	0
7	Boc	Allyl	-	0
8	Me	Me	-	0
9	Bn	Boc	-	0
10	Bn	Bn	-	0
11	Boc	Boc	**322**	62

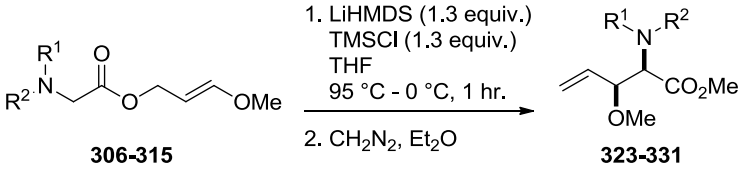
Couplings utilizing isopropoxy allylic enol ether **284** were somewhat limited. Coupling with *N*-Boc sarcosine (Entry 1) and *N*-methoxy carbamate sarcosine (Entry 2) were successful affording the desired allylic amino esters. However, a significantly reduced

yield was achieved in comparison to the methoxy derived allylic amino ester. Interestingly, none of the desired product was obtained when utilizing *N*-Cbz sarcosine (Entry 3). Switching to the tosyl protected sarcosine (Entry 4), the desired product was obtained, however significant levels of impurities were also obtained. Several attempts at purification were examined, including more acid/base washes, flash chromatography on deactiviated silica and basic alumina and finally a Kugelrohr bulb-to-bulb distillation, with none improving the purity of the allylic amino ester. Both the acetamide and trifluoroacetamide protected sarcosine (Entries 5 & 6), failed to deliver the desired product, with an intractable mixture being achieved for the acetamide, whilst similar degradation products seen in with the methoxy derivatives was seen when using trifluoroacetamide. Utilizing *N*-boc allyl glycine (Entry 7) only the parent amino acid was recovered. When investigating the amino acids containing two of the same protecting groups, only one, *N*-diboc glycine coupled in 20%. It was observed that this allylic amino ester was sensitive to acid, so therefore, repetition of the coupling, omitting the citric acid wash increased the yield to a more synthetically useful 62%. After this observation, all allylic amino esters couplings that failed utilizing the isopropoxy allylic enol ether **284** were repeated, omitting the acid wash, however, still none of the desired allylic amino ester was yielded.

3.1.3 *Rearrangements*

With the allylic amino esters in hand, investigation of the rearrangements took place (Table 14). Initial investigation of the rearrangement different protected nitrogens will be based upon the optimized conditions developed for the *N*-phthalimide protected substrates.

Table 14: Methoxy derived allylic amino ester rearrangements



306-315 **323-331**

Entry	Allylic amino ester	R^1	R^2	Product	Yield (%)[a]	dr[b] (*syn*:*anti*)
1	**306**	Boc	Me	**323**	73	2:1
2	**307**	CO_2Me	Me	**324**	42	1:1
3	**308**	Cbz	Me	**325**	41	2:1
4	**309**	Ts	Me	**326**	70	1:1
5	**310**	Ac	Me	**327**	58	1:1
6	**311**	Boc	Allyl	**328**	73	2:1
7	**312**	Boc	Bn	**329**	57	4:1
8	**313**	Bn	Bn	-	0[c]	-
9	**314**	Boc	Boc	**330**	40	>25:1
10	**315**	*N*-Boc Proline		**331**	95	>25:1

[a] Isolated yield. [b] Diastereomeric ratio measured by ^{1}H NMR analysis of crude reaction mixtures. [c] Starting allylic amino ester recovered in >95%.

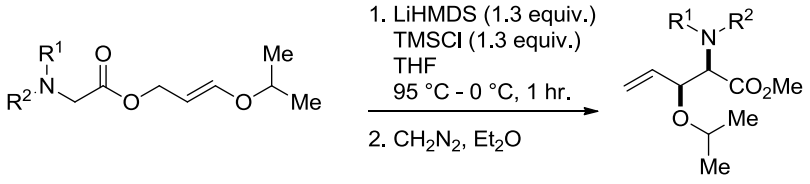
In common with the starting allylic amino esters, rearranged products that contained a carbamate protecting group, except for *N*-diboc glycine were obtained as a rotameric mixture. The Boc-sarcosine based allylic amino ester (Entry 1) successfully rearranged to the desired product in a comparative yield to the phthalimide protected allylic amino ester **229**, however, the diastereoselectivity of the rearrangement was significantly reduced. This trend in reduction of diastereoselectivity was also observed with other carbamate protected sarcosinate allylic amino esters (Entries 2 & 3), however, a significant decrease in isolated yield was also observed in these cases.

Changing to a sulfonamide (Entry 4), offered no selectivity with a 1:1 diastereomeric mixture being obtained. An acetamide (Entry 5) also offered no selectivity. *N*-Boc, allyl allylic amino ester (Entry 6), affords the rearranged product in a comparative yield to some of the earlier investigated substrates, however once more, limited selectivity was observed. Importantly, the incorporation of the allyl group, not only serves as a

protecting group, but also as a functional handle, for the further manipulation of the rearranged products (*vide infra*). *N*-Boc benzyl allylic amino ester (Entry 7) showed an increase in diastereoselectivity, however the observed levels were significantly lower than those observed utilizing *N*-phthalimide allylic amino esters. The rearrangement of the *N*-dibenzyl based allylic amino ester (Entry 8), none of the rearranged product was observed under these conditions. Instead a quantitative return of the allylic amino ester was obtained. Switching to a *N*-diboc glycinate (Entry 9), complete conversion of the allylic amino ester is once again not observed, with only the starting allylic amino ester and the rearranged product being obtained, with the rearranged product as a single diastereomer.

Similarly, the rearrangements of the isopropoxy derived allylic amino esters were investigated (Table 15).

Table 15: Isopropoxy derived allylic amino ester rearrangements



320-322 **332-334**

Entry	Allylic amino ester	R^1	R^2	Product	Yield (%)[a]	dr[b] (*syn*:*anti*)
1	**320**	Boc	Me	**332**	62	2:1
2	**321**	CO_2Me	Me	**333**	66	1:1
3	**322**	Boc	Boc	**334**	35	>25:1

[a] Isolated yield. [b] Diastereomeric ratio measured by ^1H NMR analysis of crude reaction mixtures.

Rearranged products containing a carbamate protecting groups, except for *N*-Diboc glycine were obtained as rotameric mixtures. Pleasingly all three allylic amino esters rearranged successfully to the corresponding β-isopropoxy α-amino ester after methylation.

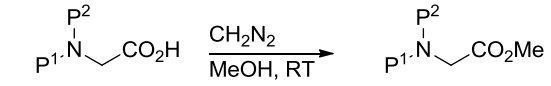
When either a tertiary butyl or a methyl carbamate (Entries 1 & 2) protected nitrogen was employed little to no selectivity was observed. Switching to *N*-Diboc glycinate (Entry 3), complete diastereoselective control was observed with the rearranged product being obtained as a single diastereomer, with no other side products.

All three of these results are directly comparable to the respective methoxy derived allylic amino esters.

It has been clearly demonstarted that changing the nitrogen protecting groups has a significant effect upon the developed rearrangement. These effects range from allylic amino ester synthesis, all the way through to the diastereoselectivity achieved upon rearrangement. The highest diastereoselectivites were achieved when using two carbonyl based protecting groups. Since the diastereoselectivity of the rearrangement is based solely upon the geometry of the SKA formed, and as the allylic geometry is fixed (*vide supra*, Scheme 50) changing the protecting group of the nitrogen is likely to influence the selectivity of the SKA formation.

3.2 SILYL KETENE ACETAL (SKA) INVESTIGATION

Due to such a large variation in diastereoselectivity observed for differently protected amino acids, it was decided to investigate the ratio of geometries of SKAs being formed. It was foreseen that there would be a direct correlation between the *E*/*Z* geometry of the SKA formed and the observed diastereoselectivity in the rearrangement. This in turn will allow determination of actual reaction pathway, whether its going through a truly concerted mechanism; a [3,3]-sigmatropic rearrangement, or a non-concerted mechanism and reacting *via* aldol type reactions. Due to the ^{1}H NMR resonance of the SKA proton, investigations using our allylic amino esters such as **229** or **314**, would be futile due to an overlap of the starting allylic ester signals, of rearranged material and the SKA signals, therefore making the assignment and determining the selectivity of the SKA formation tricky. Instead, since the rearrangement utilizes primary allylic esters, test substrates as the methoxy amino esters were prepared and isolation of the SKAs were investigated. The three test substrates were prepared by treating the required amino acid with an excess of diazomethane to form the required methoxy ester (Scheme 102).



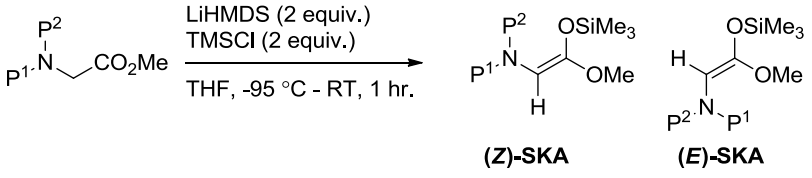
228 $P^1 = P^2$ = Phth
294 P^1 = Boc, P^2 = Me
305 $P^1 = P^2$ = Boc

232 $P^1 = P^2$ = Phth **58%**
335 P^1 = Boc, P^2 = Me **74%**
336 $P^1 = P^2$ = Boc **54%**

Scheme 102: Preparation of test substrates

With the three methoxy esters in hand, each was subjected to LiHMDS in the presence of TMSCl at -95 °C before warming to room temperature. Samples were rapidly concentrated and assayed by ^{1}H NMR to determine the SKA geometry ratio (Table 16).

Table 16: SKA investigation



232 $P^1 = P^2$ = Phth
335 P^1 = Boc, P^2 = Me
336 $P^1 = P^2$ = Boc

337 $P^1 = P^2$ = Phth
338 P^1 = Boc, P^2 = Me
339 $P^1 = P^2$ = Boc

Entry	Substrate	SKA/SM	Mass Return (%)	*Z*/*E*	Rearrangement dr (OMe, *syn*:*anti*)
1	**232**	7:1	99	12:1	11:1
2	**335**	4:1	100	2:1	2:1
3[a]	**335**	4:1	95	2:1	2:1
4	**336**	1:3.5	72	>25:1	>25:1

[a] 6 equivalents of TMSCl used and allowed to warm to room temperature over 4 hours.

Isolation of the SKA was successful in all cases with the major isomer being confirmed as the (*Z*)-SKA through NOeSY experiments (Appendix 7.2.1). This confirms that the rearrangement takes places, *via* the (*Z*)-SKA. Due to an observed *syn*-selectivity this suggests rearrangement takes place through a chairlike transistion state. Changing the nitrogen protecting groups (Entries 1, 2 & 4) has a dramatic effect on the selectivity of SKA formation. When di-Boc protection is employed (Entry 4) only a fraction of the starting amino ester is consumed to the SKA when the reaction is initiated at -95 °C

agreeing with the significant quantities of unreacted starting allylic amino ester **314** being isolated after rearrangement after one hour. Moving to the Boc-sarcosine methyl ester (Entry 2), selectivity between the two SKAs is minimal, with only a 2:1 ratio being formed. The use of additional equivalents of TMSCl and increasing the reaction time to four hours (Entry 3), leads to no improvement in the selectivity. Importantly, in all cases the ratio of (*E*)/(*Z*)-SKA directly relates to the diastereoselectivity seen in the rearrangement of the methoxy based allylic amino ester. This in turn confirms that the rearrangement proceeds *via* a concerted mechanism through a chairlike transition state.

It is clear to see that there is a correlation between the SKA ratios and the diastereoselectivity observed within our rearrangement. However rational behind this correlation is unknown at the present time.

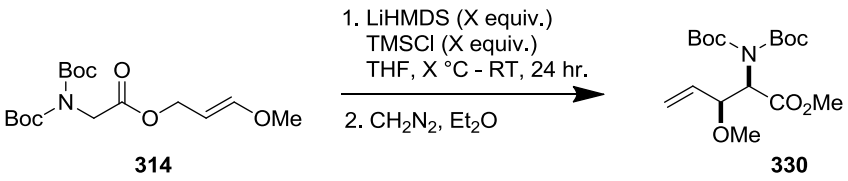
3.3 DIBOC SUBSTRATES

Using *N*-Diboc glycine as the amino acid coupling partner, rearrangement was observed to form a single diastereomer in both the methoxy and isopropoxy derived allylic amino esters. This has been supported by the isolation of a single SKA geometry, however further investigation into the scope of using *N*-Diboc amino allylic esters is required to determine whether this is applicable to other substrates. Prior to investigating the scope, an optimization of the reaction conditions was carried out in order to increase the yield.

3.3.1 *Diboc optimization*

Although successful rearrangement of allylic amino ester **314** to amino ester **330** was observed, complete conversion of the starting allylic amino ester was not. More importantly, isolation of the desired product from the remaining allylic amino ester is not possible by flash chromatography due to co-elution of both starting allylic amino ester and product. Also a strong desire to increase the isolated yield to one more synthetically useful, led to an optimization of reaction conditions (Table 18).

Table 18: Rearrangement optimization



314 **330**

Entry	LiHMDS (equiv.)	TMSCl (equiv.)	Temp. (°C)	Conversion [c] (%)	Yield [d] (%)	dr [e] (*syn*:*anti*)
1 [a]	1.3	1.3	-95	60	40	>25:1
2 [a]	1.3	1.3	-78	50	45	>25:1
3 [a]	2	2	-95	75	56	>25:1
4 [af]	2	2	-95	100	62	>25:1
5 [a]	2	2	-78	100	72	>25:1
6 [b]	2	2	-78	100	30	>25:1

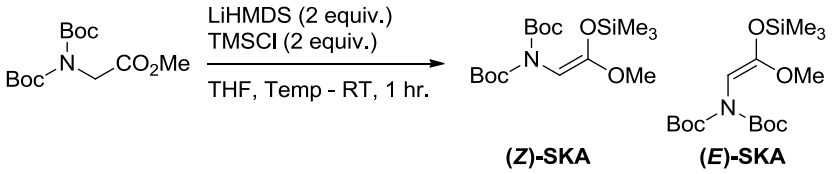
[a] Syringe pump: addition via syringe pump at 3 mL/min. [b] Hand: addition by hand over 20 seconds. [c] Measured by ^{1}H NMR analysis of crude reaction mixtures after 24 hours. [d] Isolated yield. [e] Diastereomeric ratio measured by ^{1}H NMR analysis of crude reaction mixtures. [f] time = 72 hours

After repetition of the original protocol over an extended time period (Entry 1), a slight increase in conversion was observed (60% *cf.* 45%) however the isolated yield remained constant at 40%, this prompted us to investigate several other variables starting with the temperature of reaction initiation (Entry 2). Initiating the rearrangement at -78 °C, a greater isolated yield as a single diastereomer was obtained, however a reduction in conversion was observed. Therefore it was decided to increase the equivalents of base used. Allylic amino ester **314** was subjected to two equivalents of LiHMDS at -95 °C, and reacted for 24 hours (Entry 3) and 72 hours (Entry 4) respectively. In both cases, utilizing more base offered improved conversion of the starting allylic amino ester. With the increase in reaction time, complete conversion was seen, however this reaction time was less then desirable. Repetition of greater equivalents of base was carried out at -78 °C over 24 hours (Entry 5). Complete conversion of the starting allylic amino ester was observed during this time period, along with an increase in isolated yield to 72%. One final variation was carried out to determine the sensitivity of the reaction to rapid base addition (Entry 6). Utilizing the optimized conditions (Entry 5), LiHMDS was added by hand over 20 seconds, rather than by syringe pump at 3mL/min. Unlike with

the phthaloyl derived allylic amino ester **229**, no reduction in diastereoselectivity was observed, however a significant reduction in the isolated yield was observed.

Once more a SKA investigation was attempted, investigating the difference in SKA formation, dependant upon the temperature of initiation (Table 19).

Table 19: SKA investigation of initiation temperature



(*Z*)-SKA (*E*)-SKA

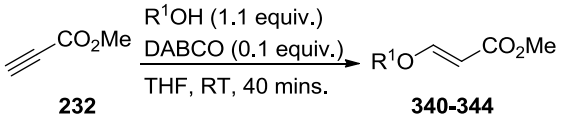
Entry	Temp (°C)	SKA/SM	Mass retur (%)	*Z*/*E*	Rearrangement dr (OMe, *syn*:*anti*)
1	-95	1:3.5	72	>25:1	>25:1
2	-78	1.4:1	89	>25:1	>25:1

From the SKA investigation it has been observed that initiation of the reaction at a higher temperature (Entry 2) immediately generates a significantly greater quantity of the SKA, and therefore, coupled with an extended reaction time, allowed for complete consumption of the allylic amino ester substrate.

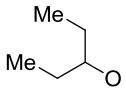
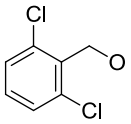
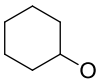
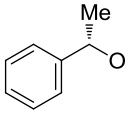
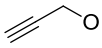
3.3.2 *Diboc substrate synthesis*

Having optimized the rearrangement, the generality was investigated using several of the allylic enol ethers previously synthesized, along with several derived from secondary alcohols. Firstly, new vinylogous carbonates were synthesized by a DABCO catalysed 1,4-additon of alcohol to methyl propiolate **232** (Table 20).

Table 20: DABCO catalyzed 1,4-addition into methyl propiolate



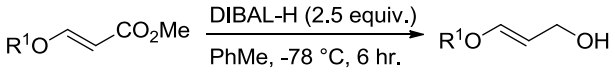
232 **340-344**

Entry	OR^1	Product	Yield (%)	Entry	OR^1	Product	Yield (%)
1		**340**	75	**4**		**343**	62
2		**341**	23	**5**		**344**	81
3		**342**	98				

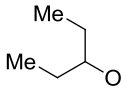
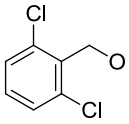
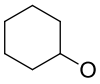
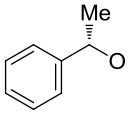
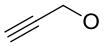
Due to the successful synthesis and rearrangement of the isopropoxy derived allylic amino ester, other secondary alcohols were also successfully reacted with methyl propiolate. Isopentyl alcohol (Entry 1) and cyclohexyl alcohol (Entry 2) were both successfully reacted with methyl propiolate to form the desired vinylogous carbonates. Cyclohexyl alcohol yielded the desired product in a significantly reduced yield in comparison to all other DABCO catalyzed 1,4-additions. Moreso,the product was significantly more sensitive than previously synthesized products. One secondary system, comprising of a chiral α-carbon was synthesized using (*S*)-1-phenyl ethanol to allow for the investigation into the effects of chirality transfer within our rearrangement. Other alcohols to successfully coupled were, propargyl alcohol (Entry 3) where upon rearrangement will deliver a terminal alkyne, suitable for enyne metathesis reactions, whilst 2,6-dichlorobenzyl alcohol (Entry 4) would act as a protecting group, which is particularly susceptible to dry acid.

Following the synthesis of the vinylogous carbonates, DIBAL-H reduction afforded the allylic enol ethers (Table 21).

Table 21: Vinylogous ester reductions



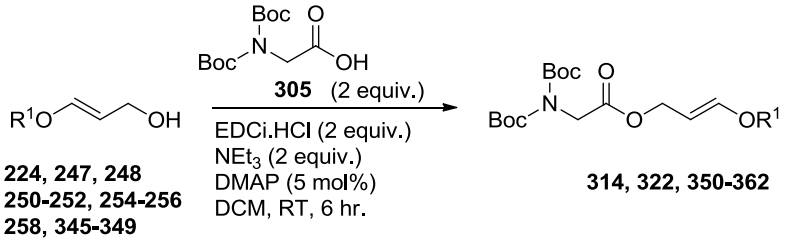
340-344 **345-349**

Entry	OR^1	Product	Yield (%)	Entry	OR^1	Product	Yield (%)
1		**345**	68	**4**		**348**	67
2		**346**	74	**5**		**349**	75
3		**347**	75				

All of the vinylogous esters were successfully reduced to the allylic enol ether in good yield (67 – 75%), with none requiring further purification. Once more, all allylic enol ethers were extremely sensitive to a wide range of conditions and suitable precautions , such as cold storage under nitrogen had to be taken to prevent rapid decomposition.

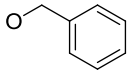
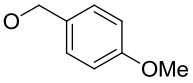
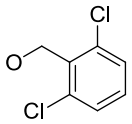
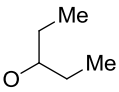
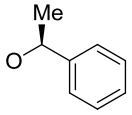
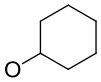
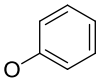
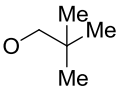
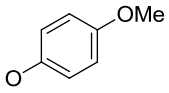
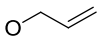
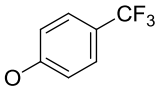
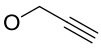
Using the optimized carbodiimide promoted protocol the desired allylic amino esters were synthesized from *N*-Diboc glycine (Table 22).

Table 22: Allylic amino ester synthesis



224, 247, 248
250-252, 254-256
258, 345-349

314, 322, 350-362

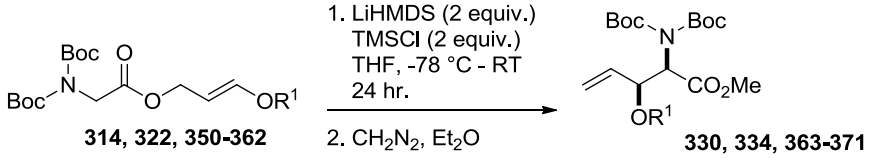
Entry	Allylic enol ether	OR^1	Yield (%)	Product	Entry	Allylic enol ether	OR^1	Yield (%)	Product
1	**224**	OMe	70	**314**	**9**	**252**		63	**356**
2	**247**	OEt	91	**350**	**10**	**254**		70	**357**
3	**248**		62	**322**	**11**	**348**		94	**358**
4	**345**		75	**351**	**12**	**349**		49	**359**
5	**346**		45	**352**	**13**	**255**		95	**360**
6	**250**		71	**353**	**14**	**256**		79	**361**
7	**251**		78	**354**	**15**	**258**		96	**362**
8	**347**		85	**355**					

All of the allylic enol ethers coupled in good yield (45 – 96%), however not all of the couplings were sufficiently high in purity to use in the rearrangement. The benzyloxy derived substrate **357** required flash chromatography on basic alumina, whilst purification of the cyclohexyl derivative **346** was even more detrimental, therefore the allylic amino ester was taken through crude and immediately subjected to the rearrangement protocol. Suitable precautions such as cold storage under nitrogen were also taken to prevent decomposition.

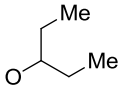
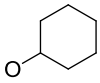
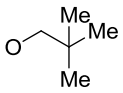
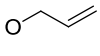
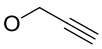
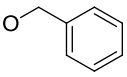
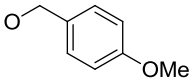
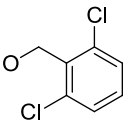
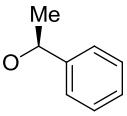
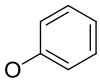
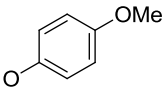
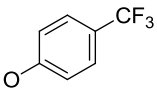
3.3.3 *Diboc substrate rearrangement*

With a wide range of allylic amino esters in hand, the scope of the rearrangement could be investigated utilizing the optimized rearrangement protocol (Table 23).

Table 23: Scope of enol ether in rearrangement



314, 322, 350-362 **330, 334, 363-371**

Entry	Allylic amino ester	OR^1	Product	Yield(%)[a]	dr[b] (*syn*:*anti*)
1[c]	**314**	OMe	**330**	72	>25:1
2[c]	**350**	OEt	**363**	56	>25:1
3[c]	**322**		**334**	50[d]	>25:1
4[c]	**351**		**364**	45[e]	>25:1
5[c]	**352**		-	0[f]	-
6[c]	**353**		**365**	80	>25:1
7[c]	**354**		**366**	65	>25:1
8[c]	**355**		**367**	71[g]	>25:1
9[c]	**356**		**368**	55	>25:1
10[c]	**357**		**369**	40[h]	>25:1
11[c]	**358**		**370**	78	>25:1
12[c]	**359**		**371**	42	2.25:1
13[c]	**360**		-	0[f]	-
14[c]	**361**		-	0[f]	-
15[c]	**362**		-	0[f]	-

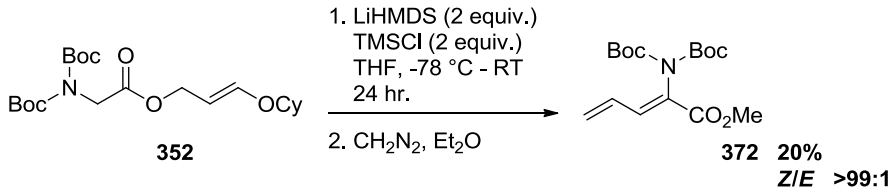
[a] Isolated yield. [b] Diastereomeric ratio measured by ^{1}H NMR analysis of crude reaction mixtures.

[c] LiHMDS solution added over 15 minutes by syringe pump. [d] 20% methyl *N*-diboc glycinate isolated

[e] 10% methyl *N*-diboc glycinate isolated [f] Only diene **272** was isolated.[g] Isolated as trimethylsilyl alkyne.

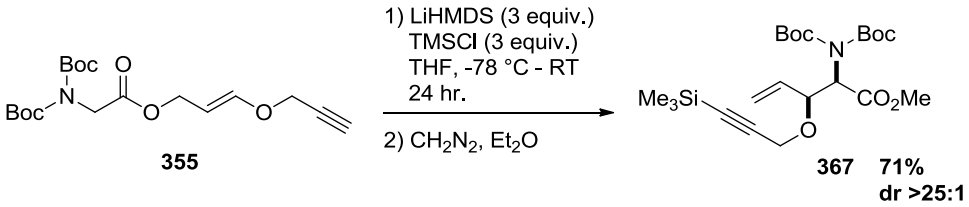
[h] 40% methyl *N*-diboc glycinate isolated [i] Starting allylic amino ester recovered in >95%.

Once more, the rearrangement is seen to be general offering yields of 42 – 80%, whilst all rearrangements proceeded with complete diastereocontrol affording the rearranged products as a single diastereomer. A large range of *O*-functionalities have been investigated and are tolerated through the synthesis of our allylic amino esters and the rearrangement, starting with simple alkyl substrates (Entries 1 & 2). Secondary ethereal systems (isopropyl, entry 3) and (isopentyl, entry 4) both rearrange in 50% and 45% respectively. Interestingly, using cyclohexyl derived allylic amino ester, didn't rearrange as expected. Instead decomposition of rearranged product to form diene **372** was observed (Scheme 103). The formation of **372** is likely to arise from a successful rearrangement followed by an $E1_{cb}$ elimination under the reaction conditions, or upon work up.



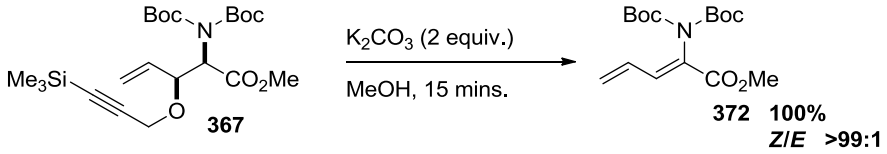
Scheme 103: Rearrangement of 352 leading to the formation of diene 372 *via* an $E1_{cb}$ elimination pathway

Access to alkylated oxygens containing a neopentyl group (Entry 6) is once more possible and is achieved in a comparable yield to the phthaloyl protected allylic amino ester **263**, whilst incorporation of the allyl group is also successful (Entry 7). Moving to the propargylic ether, different reactivity was observed. Utilizing the optimized protocol, complete conversion of the allylic amino ester was not observed. Instead, silylation of the terminal acetylene of the rearranged product was also observed, therefore increasing the equivalents of LiHMDS and TMSCl to three, complete conversion of allylic amino ester **355** rearranged to afford the *C*-silylated product **367** in a 71% yield and as a single diastereomer (Scheme 104).



Scheme 104: Trimethylsilyl alkyne 367 obtained from the rearrangement of allylic amino ester 355

Subsequent silyl deprotection of the by subjecting acetylene **367** to methanolysis in the presence of potassium carbonate, was unsuccessful (Scheme 105).



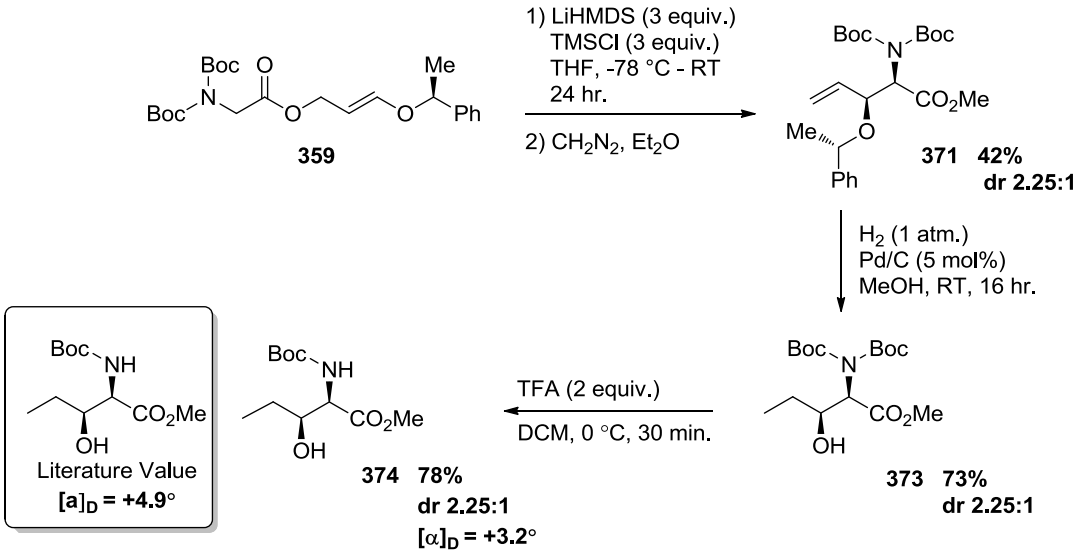
Scheme 105: Diene afforded from attempted trimethylsilyl deprotection

Diene **372** was afforded as as single product **367** in quantitative yield *via* an $E1_{cb}$ elimination similar to that seen after the rearrangement of allylic amino ester **353**.

All three benzyl protecting groups (Entries 9 – 11), were tolerated, with each affording the desired product in good yield, with the 2,6-dichlorobenyl ether in a greater synthetically useful yield.

Once again, interesting chemoselectivity was observed with the phenoxy based allylic amino esters (Entries 13 – 15), with only starting allylic amino ester being recovered. Each of these rearrangements was repeated utilizing LDA instead of LiHMDS under the same developed protocol. In all three examples, complete consumption of the starting allylic amino ester was observed, however, none of the desired product

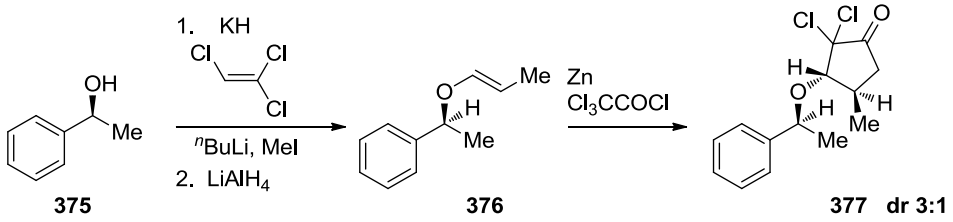
When the (*S*)-1-phenyl ethanol derived allylic amino ester **359** was rearranged, a 2.25:1 diastereomeric mixture of both *syn*-diastereomers was obtained. To determine the major product, it was required to manipulate the rearranged product to a known compound to allow a direct comparison of experimental data (Scheme 106). Firstly **371** was subjected to hydrogenolysis in the presence of catalytic palladium on carbon to afford the deprotected amino ester **373**. Subjecting **373** to TFA (2 equivalents) in DCM, mono-deprotected the amine functionality to afford the threonine analogue **374**.



Scheme 106: Rearrangement of 359 and subsequent elaboration to determine major product

Comparison of the optical rotations of the synthesized **374** and the literature value as reported by Misiti *et al.* show the same direction of optical rotation, therefore confirming the major diastereomer as **(2*R*,3*S*)-374**.[140]

The π-facial selectivity observed is similar to the selectivity observed by Greene *et al.* when they reported the use of chiral enol ethers in an asymmetric [2+2] cycloaddition for the synthesis of β-oxygenated lactones (Scheme 107).[141] Starting from (*S*)-1-phenylethanol **375** the corresponding enol ether **376** was synthesized in two steps. Subjecting **376** to a [2+2] cycloaddition with dichloroketene in the presence of zinc metal afforded β-benzyloxy cyclopentanone **377** in a diastereoselectivity of 3:1.



Scheme 107: Greene's synthesis of β-benzyloxy cyclopentanone

The extent of π-facial selectivity observed by Greene is comparable to the level of diastereoselectivity observed within rearrangement of **359** (2.25:1). Greene *et al.* rationalize their selectivity using computer simulation. It was predicted and observed that the cycloaddition takes place, in a highly selective manner on the Cα-*re* face. Applying the conformational model to the rearrangement of **359**, our observed selectivity is predicted by the transition state geometry in Figure 32.

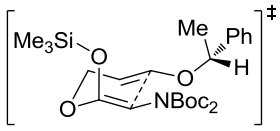


Figure 32: Plausible model for the observed diastereoselectivity in the rearrangement of chiral allylic amino ester 359

3.4 CONCLUSIONS

Utilizing several allylic amino ester substrates containing common protecting groups, a range of methoxy derived allylic amino esters have been shown to rearrange, utilizing two equivalents of LiHMDS in the presence of two equivalents pof trimethylsilyl chloride. The diastereoselectivity of the rearrangement was extremely varied, with most examples offering little to no selectivity. *N*-Diboc glycine however, rearranged with complete diastereocontrol, affording the rearranged product as a single diastereomer. Promising this observation was also seen within an allylic amino ester containing a secondary ether fragment. With such a range of diastereoselectivities being achieved, an investigation into isolating the SKA of three amino esters was investigated. All three, returned a ratio of (*E*)- and (*Z*)-SKA in direct comparison to the diastereoselectivity observed within the rearrangement of the methoxy derived allylic amino esters. Finally the scope of the *N*-Diboc glycinate allylic amino esters was investigated where a large range of ethereal functional groups were tolerated, rearranging in good yield and affording a single diastereomer. Also important to note is the selectivity achieved when rearranging allylic amino esters containing a chiral centre. Allylic amino ester **359** rearranged in 42% yield with a diastereoselectivity of 2.25:1. This level of selectivity is comparable to the selectivity observed by Greene *et al*. in their synthesis of β-oxygenated lactones.

CHAPTER 4 PRODUCT ELABORATION AND NATURAL PRODUCT SYNTHESIS

4.1 PRODUCT ELABORATION

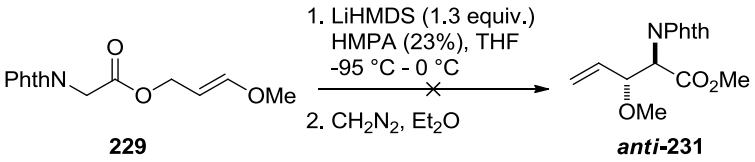
Having investigated the influence and scope of both *O*- and *N*-substitution, a number of key substrate structural features were explored. A key motivation for developing this new Ireland-Claisen protocol for the synthesis of β-hydroxy α-amino acids was the diastereo- and enantioselective control, along with the synthetic handles that are formed *in situ*. These in turn allow for synthetic conversions of these groups and for the use in natural product synthesis. To demonstrate the synthetic utility of these rearranged products, several transformations were performed.

4.1.1 *Diastereocontrol*

Synthesis of the *anti*-diastereomer as the major product would not only complement our previous work but would allow us access to either diastereomer of a desired β-hydroxy α-amino acid or ester for use in synthetic projects. There are two ways of accessing this, either by changing the geometry of the silyl ketene acetal formed or the geometry of the allylic double bond (*vide supra*). Initial attempts looked at changing the geometry of the silyl ketene acetal formed.

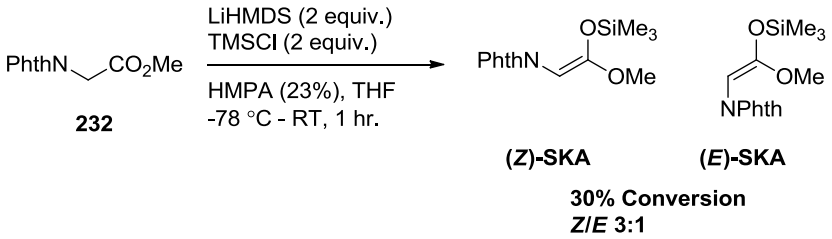
Having previously synthesized allylic amino ester **229** and subsequently rearranging to the *syn*-product **231** in high yield and diastereoselectivity, it was first investigated whether changing the geometry of the silyl ketene acetal formed would allow us access to the *anti*-diastereomer.

Subjecting allylic amino ester **229** to our optimized rearrangement conditions in the presence of HMPA, should afford the *anti*-diastereomer (Scheme 108).[95] The rate of reaction was significantly slower than observed in previous rearrangements and full consumption of the starting allylic amino ester wasn't achieved in the same time frame. Upon workup only an intractable mixture of degradation products was obtained. This is likely to be caused by the HMPA.



Scheme 108: Unsuccessful formation of the *anti*-diastereomer

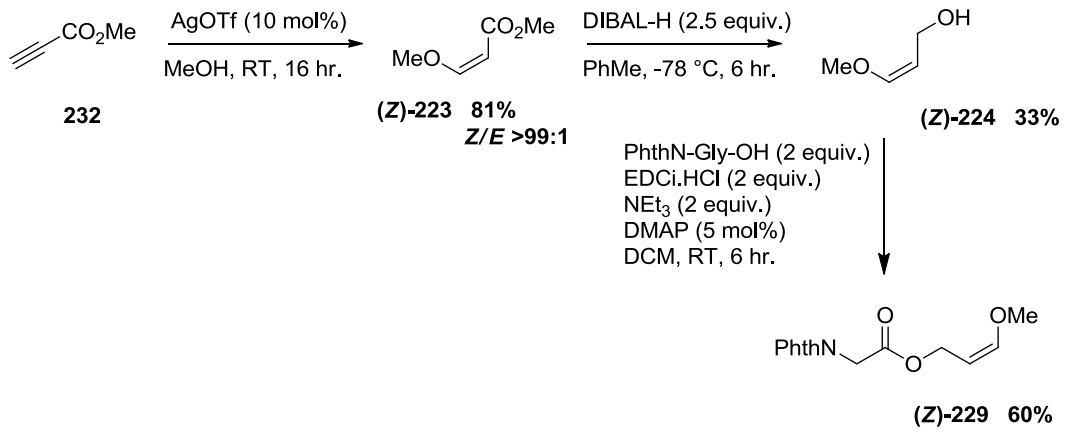
A brief investigation into the SKA that is formed under these reaction conditions was undertaken using amino ester **232** (Scheme 109).



Scheme 109: SKA investigation using HMPA

Although a significant increase in the formation of the (*E*)-SKA is observed, the (*Z*)-SKA is still the major product. Utilizing these conditions, a significantly lower conversion of amino ester **232** is observed. In addition to this, a whole series of unidentifiable side products are visible in the ^{1}H NMR spectra. With such a low conversion of the allylic amino ester to the desired (*E*)-SKA and a significant quantity of side products being formed, this clearly is not a viable route for the synthesis of the *anti*-diastereomer. Due to this, we investigated routes into the *anti*-diastereomer *via* changing the geometry of the allylic double bond.

The required (*Z*)-allylic amino ester substrate was prepared by treating methyl propiolate **232** with silver (I) triflate in methanol for 16 hours to promote a *trans*-selective addition of methanol across the alkyne to afford (*Z*)-methyl methoxyacrylate **(*Z*)-223** in a 81% and as a single geometric isomer.[142] Subsequent DIBAL-H reduction and subsequent carbodiimide promoted coupling, furnished the desired allylic amino ester **(*Z*)-229** in three steps (Scheme 110).

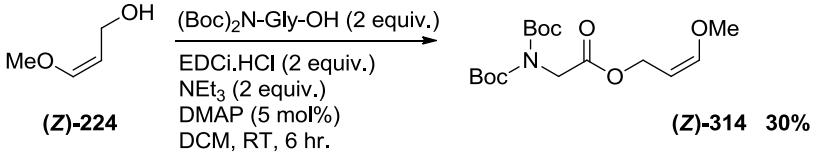


Scheme 110: Synthesis of NPhth substrate with *Z*-allylic double bond

With allylic amino ester **(*Z*)-229** in hand, rearrangement utilizing our standard conditions was attempted (Scheme 111). Again, this rearrangement required a longer reaction time and displayed a complex reaction profile in comparison to an (*E*)-allylic amino ester rearrangement. Upon work-up, an intractable mixture of starting materials, diene **284** and a small trace of the desired diastereomer was present, however neither could be isolated cleanly.

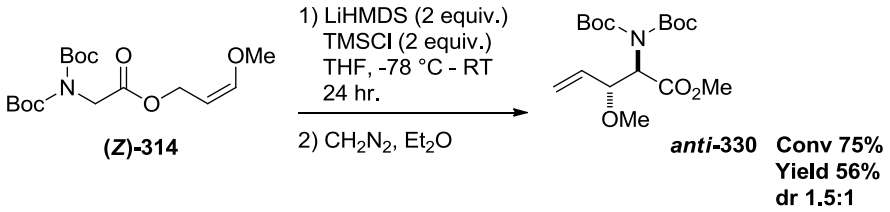
Scheme 111: Unsuccessful rearrangement of (*Z*)-229

However, due to the successful rearrangement of several di-Boc protected amino allylic ester substrates to single diastereomers, it was decided to utilize a *N*-di-Boc substrate to access the *anti*-diastereomer, hopefully with complete diastereoselective control as previously seen. Substrate **(*Z*)-313** was prepared *via* a carbodiimide coupling using allylic enol ether **(*Z*)-224** to afford the required allylic amino ester in 30% yield (Scheme 112).



Scheme 112: Synthesis of $NBoc_2$ substrate with *Z*-allylic double bond

With the required allylic amino ester in hand, the rearrangement was again investigated (Scheme 113). Utilizing the optimized conditions developed for di-Boc protected allylic amino ester substrates, rearrangement took place, again at a slower rate, with only 75% conversion of starting material within the same time frame as the (*E*)-allylic amino ester. However the reaction profile was significantly cleaner than previous attempts using HMPA or allylic amino ester **(*Z*)-229**. The rearrangement afforded amino ester ***anti*-330** as a diastereomeric mixture of 1.5:1 (*anti*/*syn*). Whilst this result is disappointing, the desired diastereomer was obtained as the major product and with further optimization of the reaction conditions, greater conversion and diastereoselectivity can hopefully be achieved.



Scheme 113: Rearrangement to the *anti*-diastereomer

A slower rearrangement with the (*Z*)-allylic enol ether, is likely to caused by a less stable chairlike transition state (Figure 33). With the (*E*)-allylic enol ether, both the large amino functionality and the enol ether are placed in favourable *pseudo* equatorial positions around the chair. Switching to the (*Z*)-allylic enol ether, the enol ether, is placed in a unfavourable axial position. This transition state is likely to be significantly higher in energy than for the **314** due to a significant 1,3-transannular interaction between the lone pairs of electrons of the SKA and the allylic enol ether.

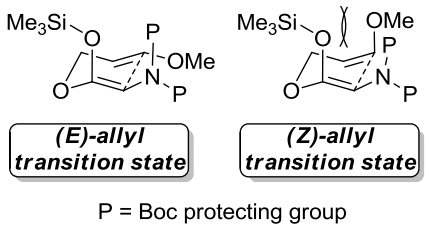


Figure 33: Comparison of transition states of the (*E*)- and (*Z*)-allylic enol ether

The generation of a mixture of diastereomers also provided an interesting result. We have observed that utilizing *N*-Diboc allylic amino ester substrates a single (*Z*)-SKA geometry is generated. Due to the synthesis of **(*Z*)-314** a single geometry of allylic

alkene has been installed. Therefore a plausible explanation to obtaining the *syn*-diastereomer is likely to be caused by the unfavourable 1,3-transannular interactions forcing the rearrangement to take place through a less favourable but possibly lower in energy boat transition state (Figure 34).

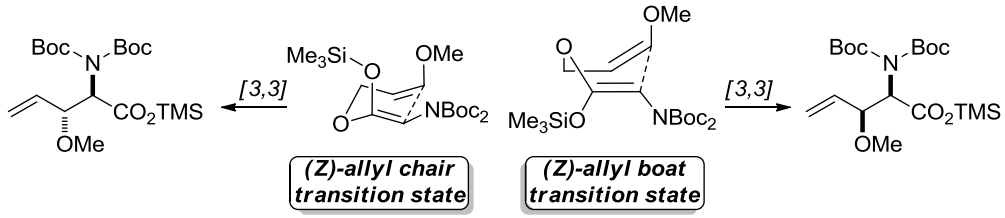
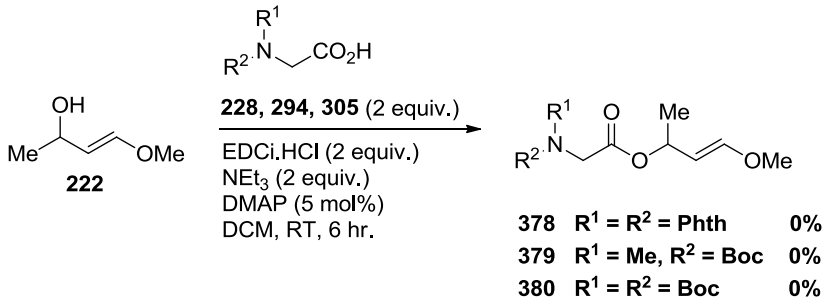


Figure 34: Chair and boat transistion states for the (*Z*)-allylic amino ester rearrangement

Alternatively, the enol ether alkene geometry may undergo interconversion from (*Z*) to (*E*) and subsequent rearrangement take place *via* a chair transition state or that a non-concerted mechanism is taking place.

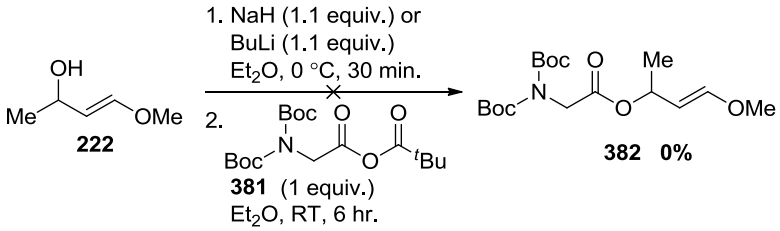
4.1.2 *Allylic enol ethers processing secondary hydroxy groups*

Expanding the scope of the allylic enol ethers to containing secondary hydroxyl groups would lead to the formation of 1,2-disubstituted alkenes. Investigation into the synthesis of this type of allylic amino ester started by taking allylic enol ether **222** under our EDCi promoted coupling utilizing several different amino acids. In all cases none of the desired allylic amino ester was obtained, although TLC analysis showed complete consumption of **222** (Scheme 114). After several attempts at each esterification either an intractable mixture of products, of which all were sensitive to purification or the starting amino acids were obtained.



Scheme 114: Attempted synthesis of allylic amino esters containing secondary hydroxy functionality *via* a carbodiimide promoted esterification

Other routes into these substrates were also investigated, including a mixed anhydride approach (Scheme 115). Irreversible deprotonation **222** to form the sodium or lithium alkoxide was followed by treatment with mixed anhydride **381** (generated *in situ* from amino acid **304** and pivaloyl chloride). Crude ^{1}H NMR analysis showed that a successful coupling reaction had taken place, however a significant number of impurities were present. Several attempts at purification, only lead to decomposition.



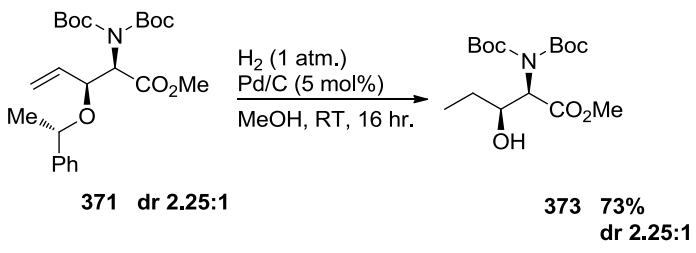
Scheme 115: Attempted synthesis of allylic amino esters containing secondary hydroxy functionality *via* a mixed anhydride approach

Previously we have shown that a *p*-nitrophenoxy derived secondary allylic enol ether **208** had previously been successfully coupled to furnished allylic amino ester **210**. Due to the unsuccessful the application of Kazmaier's protocol, it was deemed the use of an allylic aryloxy enol ether would not be applicable for this protocol.

4.1.3 *Deprotection*

4.1.3.1 *β-Hydroxyl deprotection*

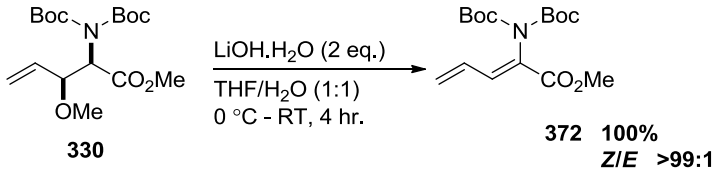
Deprotection of the β-hydroxy group affording the free hydroxyl group is important for further synthetic transformations. Subjecting product **371**, to hydrogenation conditions in the presence of catalytic palladium on carbon cleaves the 2-methyl benzyl moiety affording the free hydroxyl group as well as alkene reduction to the alkane, to afford β-hydroxy α-amino ester **373** in 73% yield (Scheme 116).



Scheme 116: Selective β-hydroxyl group deprotection

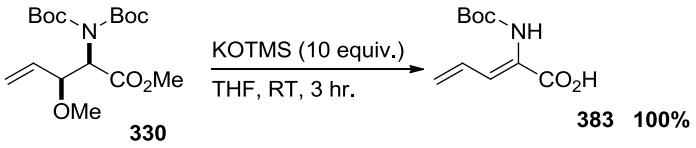
4.1.3.2 *Methyl ester deprotection*

Saponification of the ester functionality would be vital for the incorporation of the synthesized amino acid residue into peptide structures. Subjecting amino ester **330** to an alkali metal hydrolysis, similar to the one used during the amino acid synthesis, did not achieve the desired transformation (Scheme 117). Instead, a base promoted $E1_{cb}$ elimination ensued, delivering diene **372** in quantitative yield.



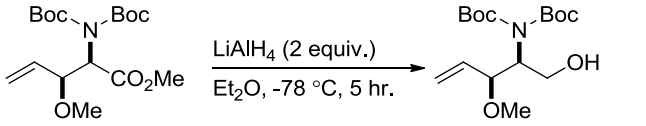
Scheme 117: Unsuccessful ester cleavage

Baldwin has reported the saponification of methyl esters using the relatively mild conditions of potassium trimethylsilanolate in a protic solvent to afford the carboxylic acid.[143] Importantly this cleavage is sufficiently mild enough to be utilized with compounds that are particularly sensitive to alkali metal hydrolysis. Following the reported procedure, amino ester **330** was treated with ten equivalents of potassium trimethylsilanolate (Scheme 118). Saponification of the ester functionality was observed, however, with such a large excess of potassium trimethylsilanolate another elimination reaction was observed. Also under these conditions, mono deprotection of the amine was observed affording diene **383** in quantitative yield. Utilizing reduced equivalents of potassium trimethylsilanolate also yielded diene **383** in a quantitative yield.



Scheme 118: Unsuccessful ester cleavage

Another useful transformation is the reduction of the ester to the primary alcohol, affording amino alcohols. Taking amino ester **330**, with lithium aluminium hydride, selectively reduces the ester to the alcohol in good yield (Scheme 119). Reduction of the ester moiety reduces the conformational restraints upon the product, and therefore a rotameric nature of amino alcohol **384** is observed.

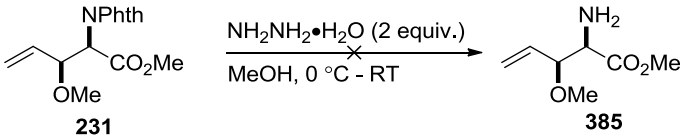


330 **384 60%**

Scheme 119: Selective reduction of the ester

4.1.3.3 *Deprotection of the amine*

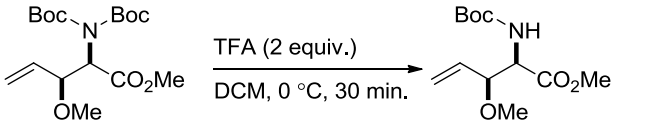
Deprotection of the amine functionality is also important for the incorporation of the β-hydroxy α-amino acid moiety into large peptide structures. Initially the deprotection of the phthalimde group was investigated. Traditionally, deprotection of phthalimde moieties is through the use of hydrazine. Following the procedure as described by Danishefsky *et al.*, amino ester **231** was subjected to hydrazine monohydrate in methanol for 3 days (Scheme 120).[144] However, none of the desired deprotected amine was achieved.



231 **385**

Scheme 120: Deprotection of the amine

Investigating the deprotection utilizing amino ester **330**, excellent selectivity was observed. Subjecting **330** to two equivalents of TFA in DCM for 30 minutes as reported by Rodríguez *et al.*, afforded mono protected amino ester **386** in 78% (Scheme 121).



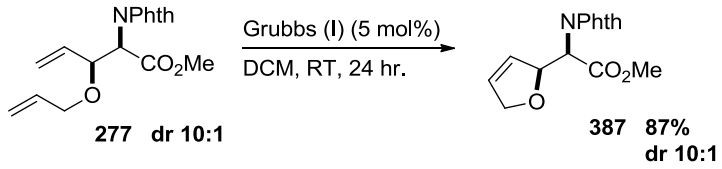
330 **386 78%**

Scheme 121: Mono boc deprotection

4.1.4 *Alkene functionalisation*

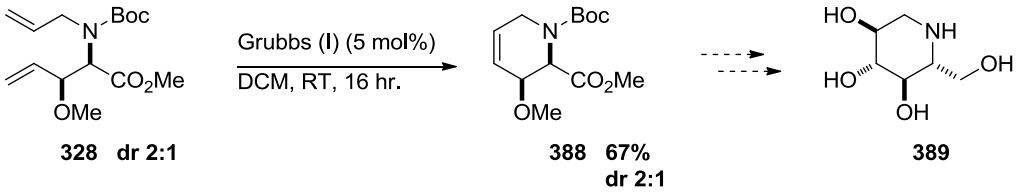
Reduction of the alkene has already been shown utilizing hydrogenation conditions (*vide supra,* Scheme 116) however, there are an appreciable number of transformations that can make use of the resultant alkene in the product. Diene **277** was subjected to a ring-closing metathesis reaction (RCM). The diene was observed to undergo efficient

ring closure when promoted by the Grubbs first-generation catalyst to form dihydrofuran **387** in excellent yield, without any loss of diastereoselectivity (Scheme 122). The core structure of norfuranomycin was formed during this reaction, however subsequent depropection of the methyl ester and of the phthalimide protecting group (*vide supra*) were ineffective, leading to decomposition products or incomplete removal of the protecting groups.



Scheme 122: RCM to form protected norfuranomycin

Another RCM has been shown using *N*-Boc, allyl glycine as the parent amino acid in the rearrangement. Again, subjecting diene **328** to Grubbs first-generation catalyst, it was observed to undergo ring closure to afford tetrahydropyridine **388**, in good yield (Scheme 123).



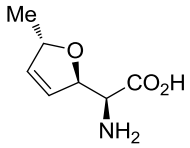
Scheme 123: RCM to form a convenient scaffold for the synthesis of iminosugars such as 1-deoxymojorimycin 389

Although a poor diastereoselectivity was achieved during the sigmatropic rearrangement, the synthetic utility of **328** allows for a rapid formation of convenient common intermediate scaffold **388** for the synthesis of iminosugars such as 1-deoxynojorimycin **389**, should an appropriate protecting group be used on the β-hydroxy moiety rather than the methoxy derivative.

4.2 NATURAL PRODUCT SYNTHESIS

4.2.1 *Furanomycin*

Furanomycin **390** (Figure 35), a naturally occurring α-amino acid containing a dihydrofuran ring was first isolated by Katagiri *et al.* in 1967 from *Streptomyces threomyceticus*.[145] Initial biological screening by Katagiri showed furanomycin to be active against several species of bacteria.[145]



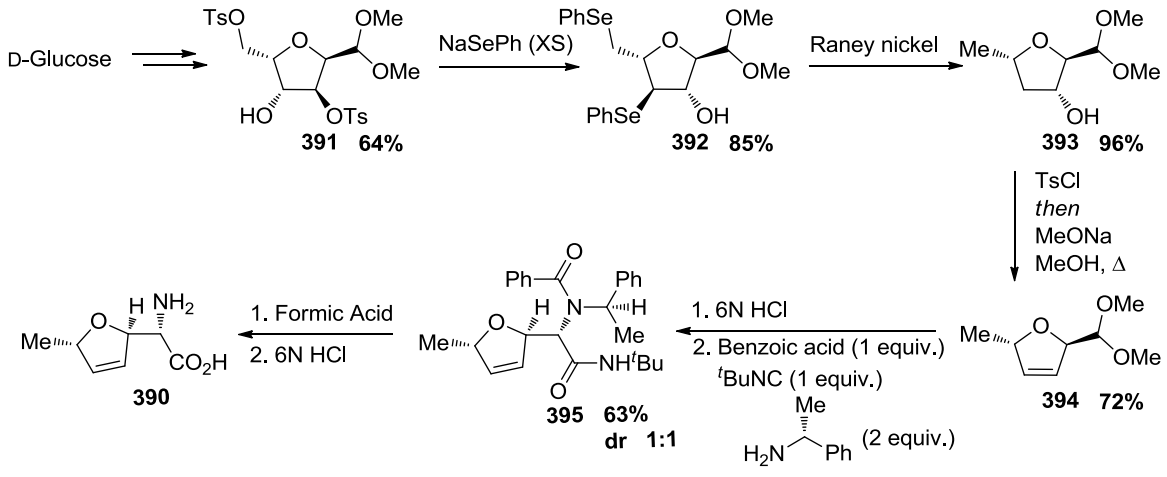
390

Figure 35: Furanomycin

Following extensive biological analysis furanomycin has been shown to demonstrate excellent antibiotic activity as well as being one of the smallest natural antibiotic products.[146] The antibiotic nature arises from the *in vitro* incorporation of furanomycin into proteins as a substitute for isoleucine.[147]

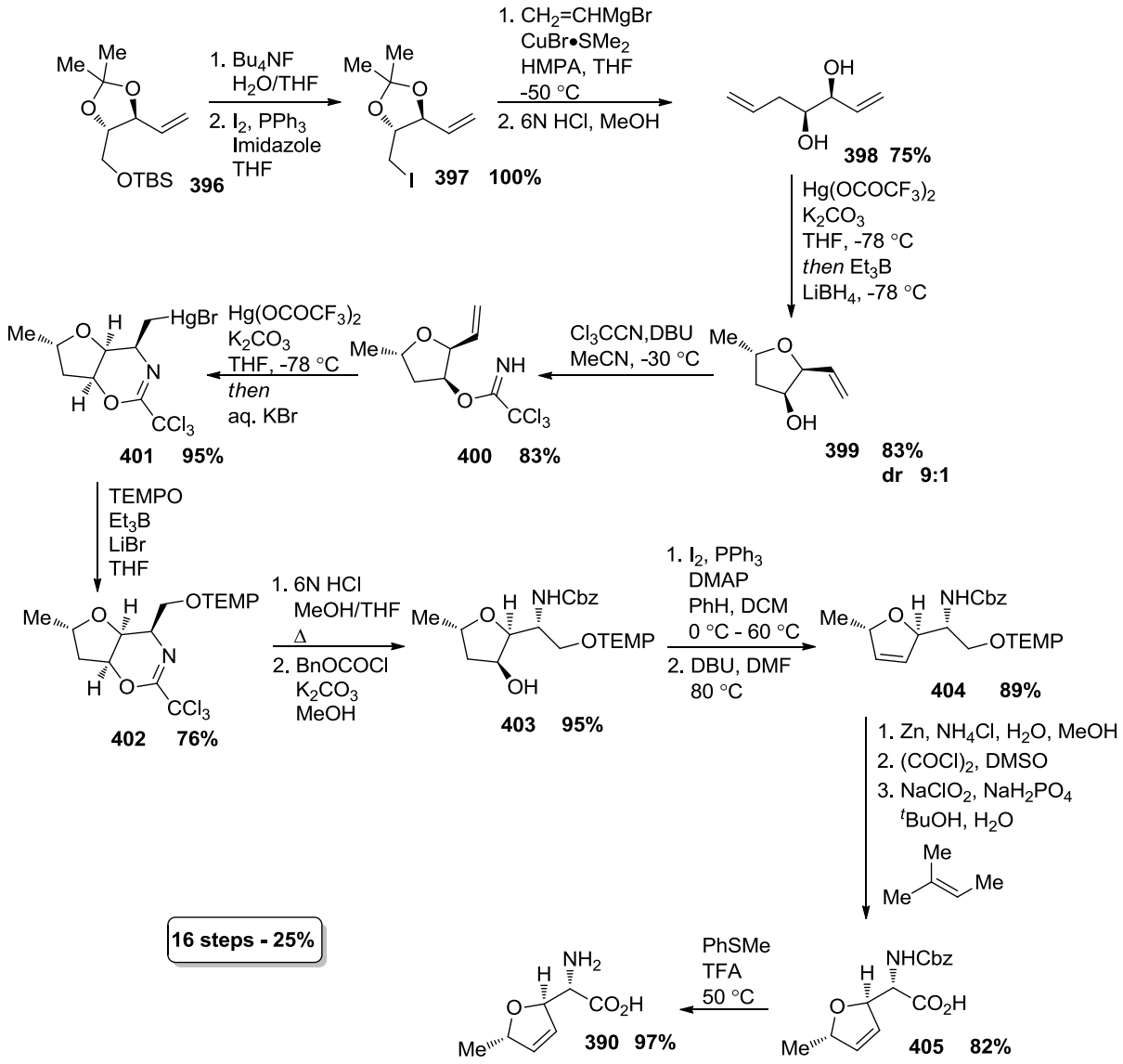
4.2.2 *Previous Syntheses*

To date, several syntheses of furanomycin and derivatives thereof have been reported, including that by the group of Joullié, who reported their synthesis in 1980 (Scheme 124).[148] Starting from D-glucose, furanose **391** was prepared following the procedure detailed by Ogawa *et al*.[149] Treatment with excess sodium phenylselenide afforded **392**, and subsequent exposured to Raney nickel, reductively removed the phenylselenyl group. This transformation also delivered the required methyl group at C(5). Tosylation followed by base mediated elimination delivered the dihydrofuran **394**. Acid mediated acetal deprotection to the sensitive aldehyde was followed by the addition of the amine functionality *via* treatment with α-methyl benzylamine. Subsquent protection as the benzoyl amide afforded dihydrofuran **395**. No selectivity was achieved during this step, providing a 1:1 mixture of diastereomers. Chromatographic separation of the diastereomers, followed by debenzylation using formic acid and acid mediated hydrolysis lead to the formation of **390**.



Scheme 124: Joullié's synthesis of furanomycin

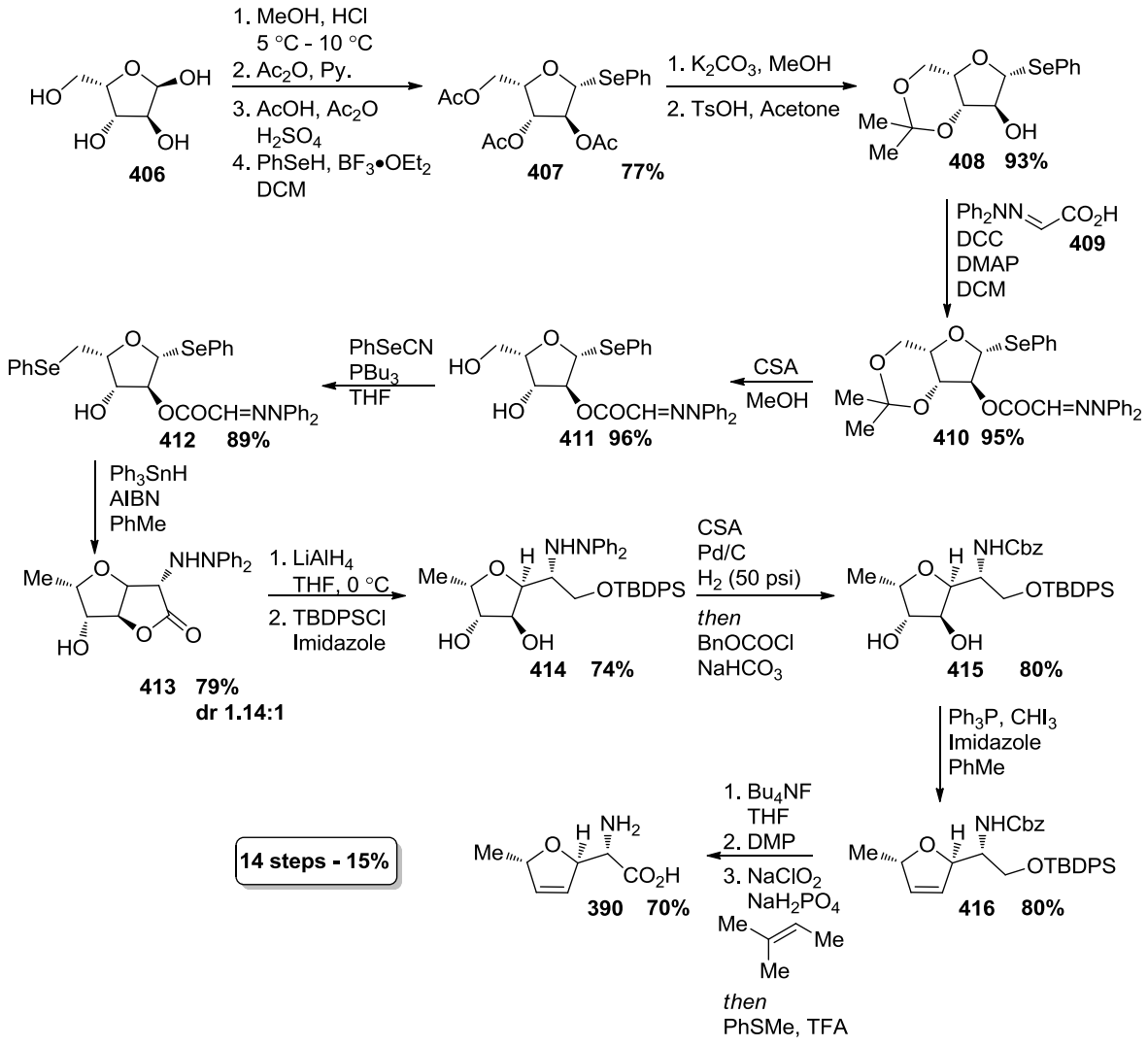
Kang *et al.* reported the first highly enantioselective synthesis in 1998 (Scheme 125).[150] The 16 step synthesis started with the deprotection of silyl ether **396**, followed by iodination yielding iodide **397** quantitatively. The addition of vinylmagnesium bromide in the presence of copper (I) bromide, followed by acetonide deprotection afforded diene diol **398**. Mercury cation mediated cyclisation followed by an *in situ* reductive demercuration afforded the tetrahydrofuran ring **399** in 83% and as an inseparable 9:1 mixture of diastereomers. Conversion to the trichloroacetimidate **400**, allowed chromatographic separation to yield the required diastereomer in 83% yield. A second mercuric cyclisation delivered **401** in 95% after an aqueous potassium bromide workup. Treatment with 2,2,6,6-trimethylpiperidine-1-oxyl (TEMPO) and lithium borohydride in the presence of triethylborane afforded the protected oxidized product **402**. Acid catalysed hydrolysis, followed by subsequent protection led to protected amino alcohol **403**. Conversion of the hydroxyl group to iodine allowed a regioselective base mediated elimination to afford the dihydrofuran ring **404**. Removal of the TEMP group and subsequent two step oxidation afforded protected product **405**. Subsequent deprotection completed the synthesis of **390** in an overall yield of 25%.



Scheme 125: Kang's synthesis of furanomycin

Clive *et al.* used a radical cyclisation approach to the synthesis of **390** (Scheme 126).[151] L-Xylose **406** was converted to its methyl glycoside, acylated, subjected to acetolysis conditions and then treated with benzeneselenol to form **407**, in a 77% yield over the four steps, without the isolation of any intermediates. Mild basic hydrolysis deprotected the hydroxyl groups before selective protection of the C(4) and C(5) hydroxyl groups as ketal **408** in good yield. Carbodiimide mediated coupling formed hydrazone ester **410**, which in the presence of acid lead to deprotection of the ketal. Selenation of the primary hydroxyl group afforded **412** which underwent a radical cyclisation to generate lactone **413**. Under these conditions, conversion of C(5) to the required methyl group was also achieved. No selectivity was observed, however isolation of the required diastereomer was possible by chromatography. Lithium aluminium hydride reduction yielded a triol

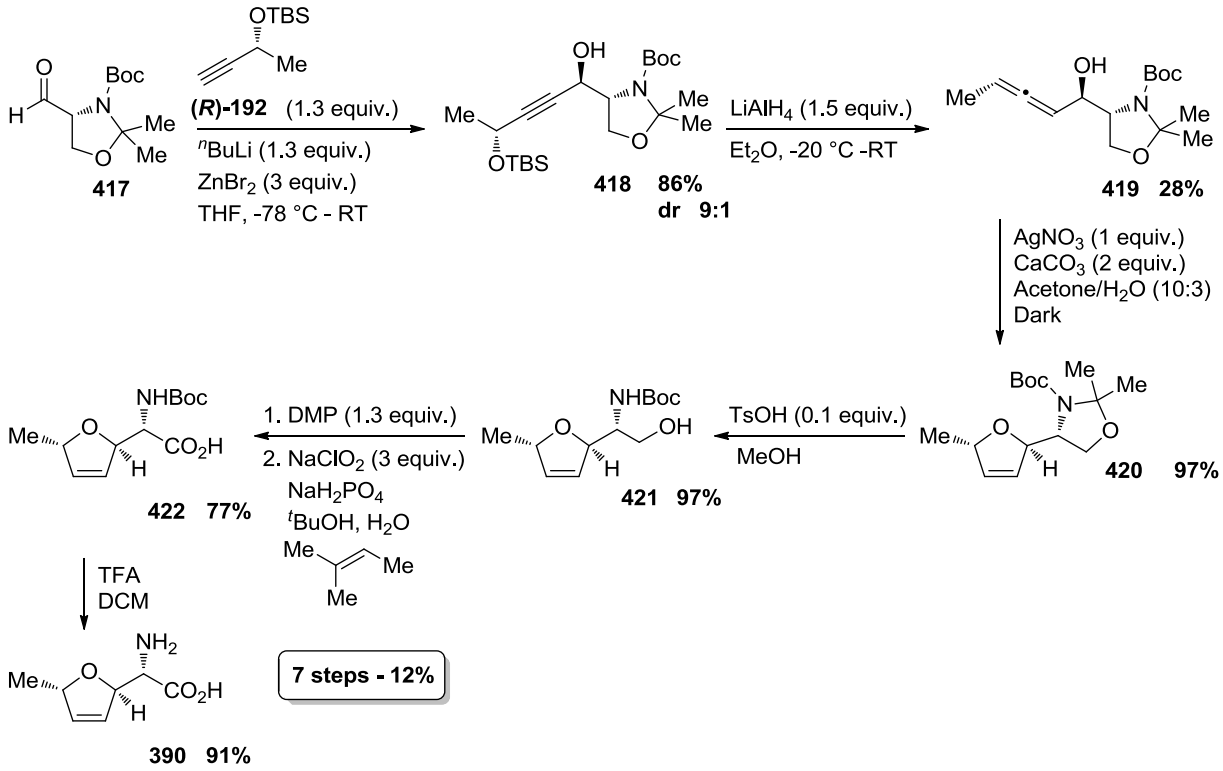
before selective protection of the primary hydroxyl group. Acidic hydrogenation followed by acylation delivered the protected amino alcohol **415**. Both remaining hydroxyl groups were removed by treatment with triphenylphosphine and iodoform to form dihydrofuran ring **416**. Hydroxyl deprotection followed by a two step oxidation and amine deprotection delivered **390** in an overall yield of 15%.



Scheme 126: Clive's synthesis of furanomycin

Standaert *et al.* reported a seven step synthesis in 2000 starting from (*R*)-Garner aldehyde **417** (Scheme 127).[152] A 1,2-additon of lithiated acetylene **(*R*)-192** to **417** in the presence of zinc bromide yielded **418** in a 9:1 mixture of diastereomers. Separation *via* flash chromatography isolated the major isomer in a 77% yield. Hydroxyl-directed reduction proved problematic with several reducing agents delivering unidentifiable products. The use of lithium aluminum hydride (6 equivalents of hydride) delivered allenic alcohol **419** in poor yield. Cyclisation of **420** proceeded smoothly in the

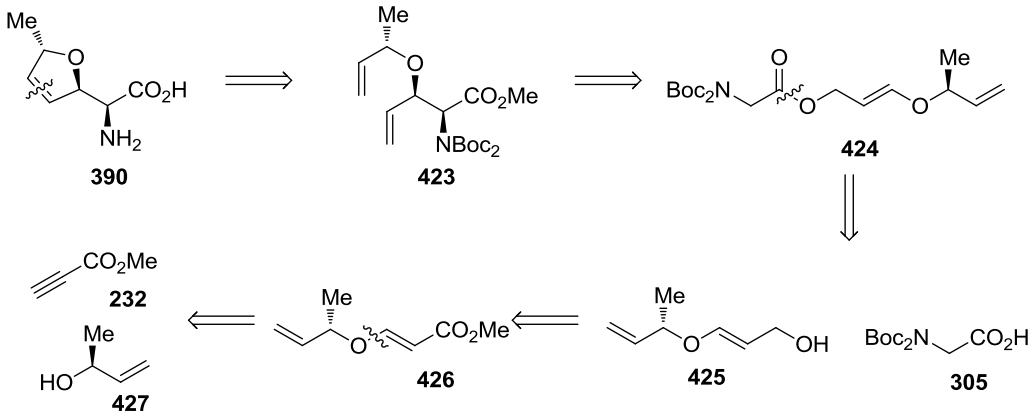
presence of silver nitrate yielding dihydrofuran **420** in almost quantitative yield. Selective *N,O*-acetonide deprotection, followed by a two-step oxidation afforded **422** and a final Boc-deprotection yielded **390**, in an overall yield of 12%.



Scheme 127: Standaert's synthesis of furanomycin

4.2.3 *Reterosynthetic analysis*

It was envisaged that the dihydrofuran ring of **390** could be installed from a RCM from diene **423**, the product of the Ireland-Claisen rearrangement of **424**. The required allylic amino ester **424** can be prepared utilizing a carbodiimide promoted coupling of **305** and **425**. Allylic enol ether **425** will be generated from a functional group interconversion of **426**, synthesized from the 1,4-addition of **427** to **232** (Scheme 128).



Scheme 128: Retrosynthetic analysis of furanomycin utilizing an Ireland-Clasien rearrangement

4.2.4 *Forward synthesis*

Due to the required enantiopure allylic alcohol not being commercially available and recent reports of the synthesis of **427** proving challenging due to its volatility, it was decided to start from allylic alcohol **428** affording substrate **429** (Figure 36).[153]

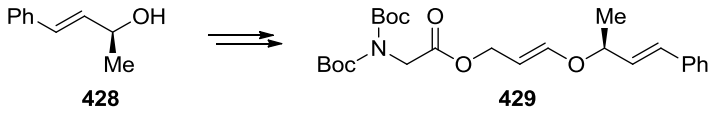
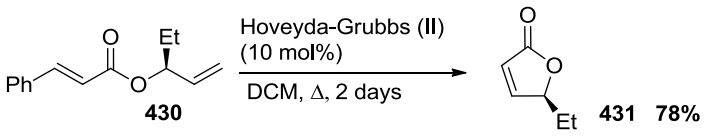


Figure 36: Required allylic alcohol and allylic amino ester

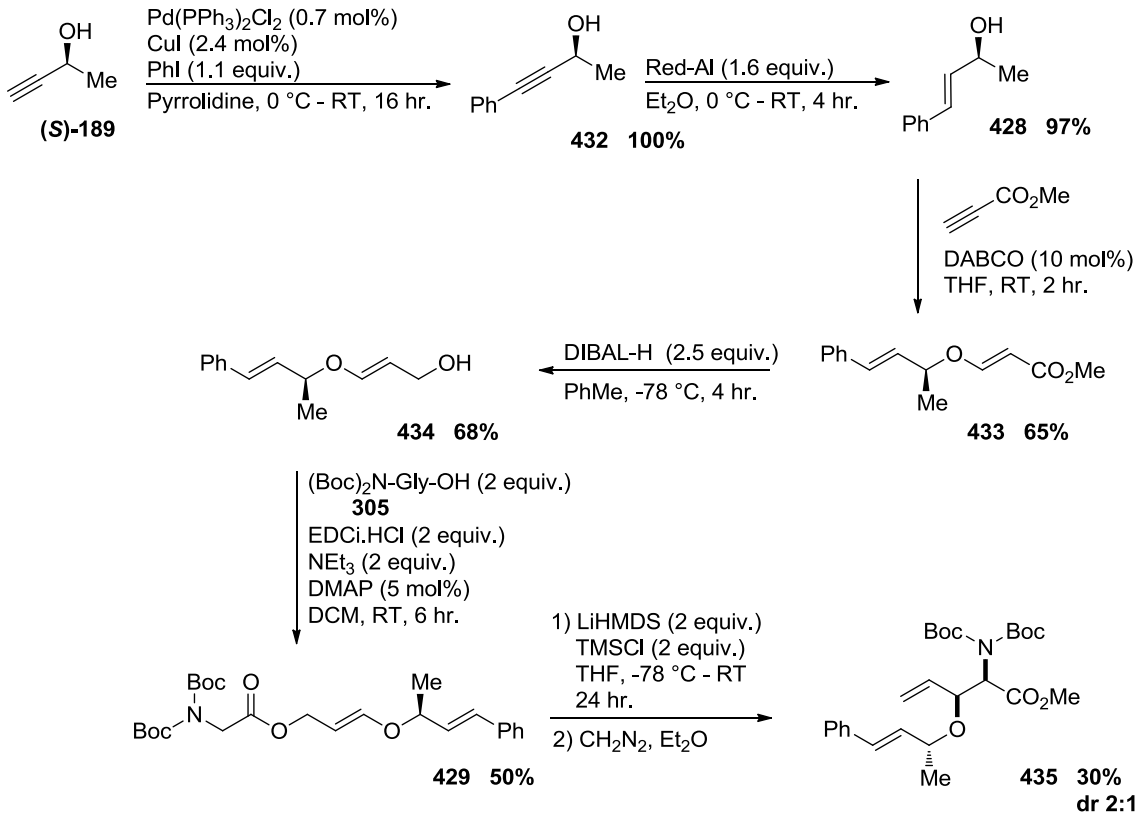
The added mass to this compound would reduce the volatility thus making allylic alcohol **428** easier to work with and the added steric bulk on the alkene should not impede the RCM significantly. Phenyl substituted alkenes such as **430** have been show to undergo facile RCM to form dihydro-γ-lactone **431** in a recent communication by Feringa (Scheme 129).[154]



Scheme 129: A recent example of a phenyl substituted alkene in a RCM

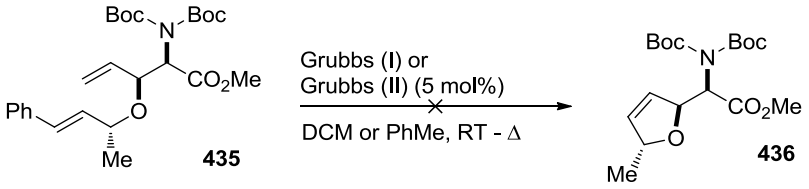
The synthesis of furanomycin started by taking (*S*)-butyn-2-ol **(*S*)-189** under Songashira coupling conditions with iodobenzene as reported by Knochel *et al.* to yield propargylic alcohol **432**, quantitatively (Scheme 130).[155] Following a reported Red-Al reduction by Ma *et al.*, reduction of the of the alkyne moiety proceed smoothly to the allylic alchol

428 in 97% yield after flash chromatography purification.[156] The 1,4-addition proceeded slowly, however returned the vinylogous ester **433** in a yield of 65%. Reduction using DIBAL-H delivered the required alkoxy allylic enol ether **434**, however significant level of unidentifiable impurities were observed. Purification by Kugelrohr bulb to bulb distillation lead to decomposition of the allylic alcohol, therefore subsequent material was taken through crude. Carbodiimde coupling yielded the required allylic amino ester **429** in a satisfactory yield. Once more this substrate proved sensitive to purification. Subjecting **429** to the developed Ireland-Claisen protocol, a successful rearrangement was observed, yielding the required diene **435** in a 30% yield and 2:1 diastereoselectivity.



Scheme 130: Synthesis of diene 435

With the required substrate in hand, we next turned our attention to the RCM to form the dihydrofuran ring (Scheme 131).

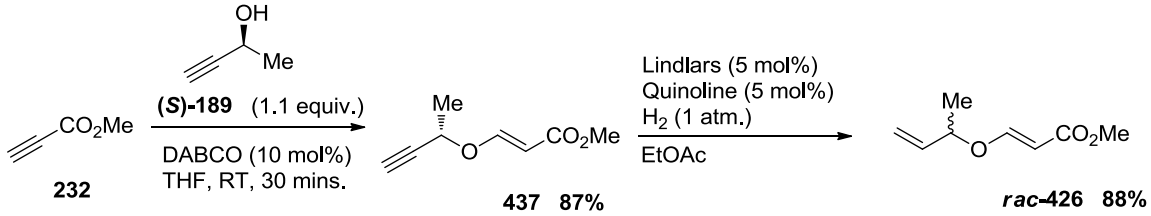


Scheme 131: Unsuccessful RCM to form dihydrofuran 436

Following the successful dihydrofuran ring synthesis (*vide supra*, Scheme 122), the same procedure was utilized in an attempt to synthesis **436**. Treating diene **435** with Grubbs first-generation catalyst in DCM at reflux did not furnish any of the desired product with only recovery of the starting diene possible. Changing the catalyst to Grubbs second-generation catalyst at reflux in toluene, still none of the desired product was observed. Finally, Hovedya-Grubbs first-generation catalyst in 10 mol% loading, at reflux in toluene was employed. Again no conversion of the starting diene **435** to dihydrofuran **436** was seen.

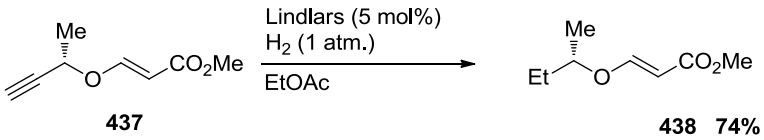
Although Feringa had reported the formation of α,β-unsaturated-dihydro-γ-lactone **431** *via* a RCM, this is the only report of a RCM containing a phenyl substituted alkene affording a 5-member ring.

Due to the lack of success with the RCM, it was decided to synthesis a substrate without steric bulk surrounding the alkene. A DABCO catalysed 1,4-addition of enantiopure (*S*)-butyn-2-ol to methyl propiolate afforded vinylogous ester **437**, in excellent yield. This in turn was also more stable and easy to handle than the required allylic alcohol. Subsequent reduction of the alkyne functionality to the required alkene was investigated. Hydrogenation using Lindlar's catalyst in the presence of quinoline yielded ***rac*-426** in 88%, however racemisation of the chiral centre was seen. Along with this 10% of over reduction to the alkane was also observed.



Scheme 132: Racemisation of the chiral centre under hydrogenation

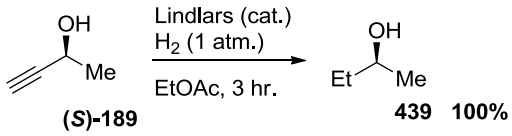
Alkyne reduction of vinylogous ester **437** was investigated without the presence of quinoline (Scheme 133). When subjected to these conditions, no selectivity was observed with reduction to alkane **438**. Interestingly, no epimerization of the chiral centre was observed. Due to the lack of selectivity or epimerization occurring alternative routes for the synthesis of vinylogous ester **426** were investigated.



437 **438** **74%**

Scheme 133: Over reduction without the use of quinoline

Direct hydrogenation of (*S*)-butyn-2-ol **(*S*)-189**, in the presence of Lindlar's catalyst, only yielded fully reduced alkane **439** (Scheme 134). In the presence of quinoline, none reduced material was isolated, possibly due to the volatility of the product.

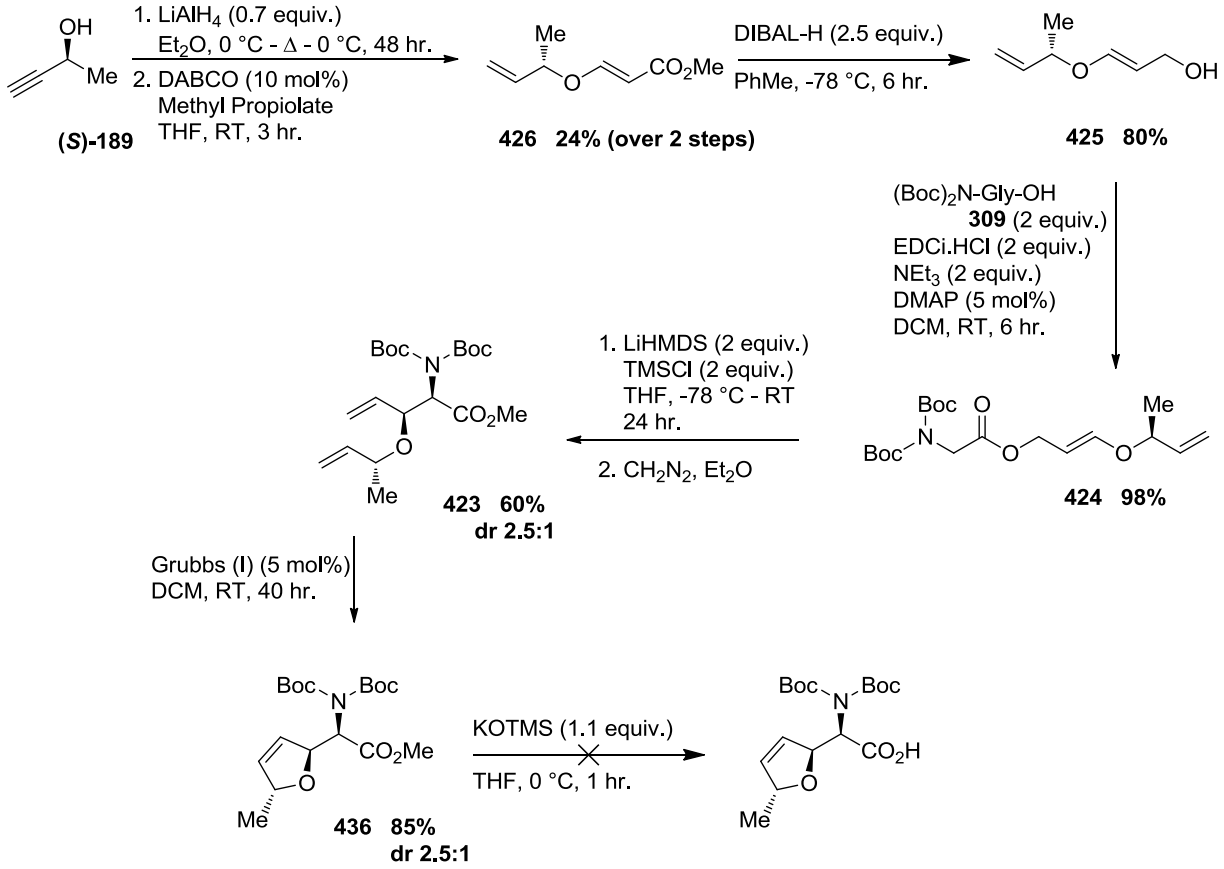


(*S*)-189 **439** **100%**

Scheme 134: Over reduction of (*S*)-butyn-2-ol

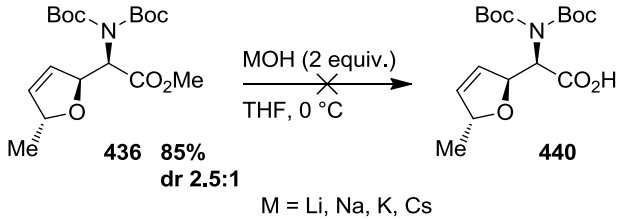
Secondly, a hydride mediated reduction of the alkyne moiety was investigated. Treating **(*S*)-189** with lithium aluminium hydride in ether at reflux for 48 hours afforded enantiopure (*S*)-buten-2-ol, in a modest yield, however comparable to literature values (Scheme 135).[153] Although complete consumption of the alkyne was not observed, no over reduction to the alkane was seen. Crude (*S*)-buten-2-ol was immediately subjected to a 1,4-addition with methyl propiolate to afford vinylogous ester **426**. It was at this stage where purification to separate the alkyne and alkene was carried out and afforded the required vinylogous ester **426** in 24% yield over the two steps. Selective reduction of **426** to the allylic enol ether afforded **425** in 80%. Carbodiimide coupling with *N*-diBocglycine **305** proceeded smoothly to afford the required allylic amino ester **424** in 98% without the need for purification. Utilizing the optimized protocol, the rearrangement was observed to be successful yielding the required diene **423** in a 60% and a 2.5:1 mixture of diastereomers. Several different conditions were tried to increase the diastereoselectivity of the rearrangement however none of these were fruitful. RCM

using Grubbs first generation catalyst was observed to be slower than previous RCMs, however the required dihydrofuran **436** was obtained in good yield and with retention of diastereoselectivity. It was at this stage that the major diastereomer was confirmed as the desired product by NOe spectroscopy due to the through space interaction between the C(5) methyl and the C(2) proton, indicating an *syn* arrangement of these two groups (Appendix 7.2.2). Subjecting **436** to potassium trimethylsilanolate resulted in decomposition of dihydrofuran **436**, with only a small trace (<5%) of unreacted **436** being isolated from the reaction.



Scheme 135: Forward synthesis of 436

Since there is a significant array of different protocols for the deprotection of methyl esters with alkali metal hydroxides in the literature, several different hydroxides were trailed to deprotect **436 (**Scheme 136).[157-159]

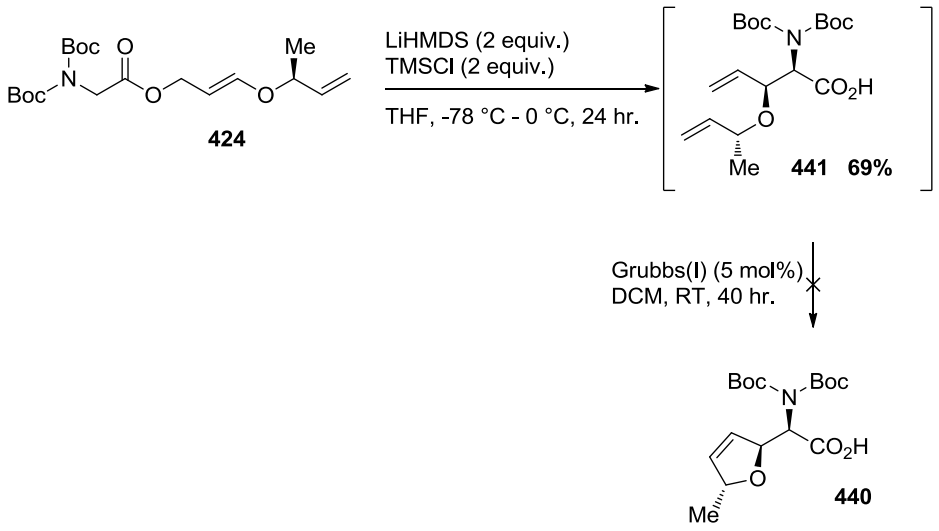


Scheme 136: Different hydrolysis approaches

In each case, none of the desired product **440** was isolated. In all four examples, complete consumption of **436** was observed by TLC analysis, although a significant number of new spots were observed. After workup, crude ^{1}H NMR analysis showed alkene signals consistent with those expected for **440**, however a vast quantity of other alkene signals and impurities were present. All attempts at purification by flash chromatography using deactiviated silica resulted in none of the desired product being isolated. Refering to the synthesis by Standaert *et al.*, after oxidation of *N*-Boc furanomycinol **421** to *N*-Boc furanomcyin **422**, no purification is used.[152] Instead the **422** is taken through crude to the final deprotection before purification. Although not stated, reasons behind this maybe the instability of **422**, leading to degradation similar to what we have observed.

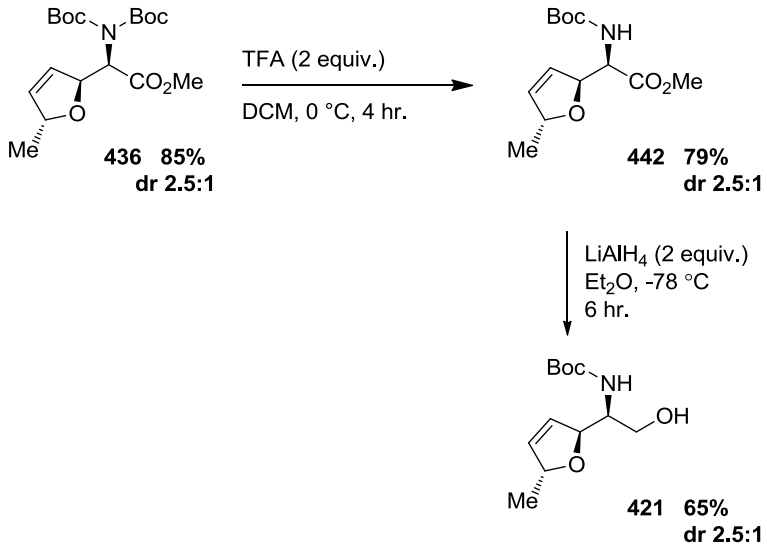
To try and follow the saponifcation closely, it was tried to monitor the reaction in a NMR tube using cesium hydroxide. Unfortunately due to the low solubility of **436** in deuterium oxide, this was not possible. Even with the addition of THF, monitoring the reaction was difficult. Instead the reaction was run as normal, and aliquots subjected to mini work-ups and immediated analysed by ^{1}H NMR. However, due to the small scale of the reaction, this method of reaction monitoring provided insufficient information about the reaction profile.

A possible route to prevent this decomposition is not adding the methyl ester therefore removing the requirement to deprotect the methyl ester. After the Ireland-Claisen rearrangement of **424**, the crude diene was isolated from the reaction mixture and immediately subjected to an RCM utilizing Grubbs first generation catalyst (Scheme 137). Unfortunately, none of the required dihydrofuran **440** was obtained. Instead, an intractable mixture of identifiable products all containing significant amounts of ruthenium based complexes making assignment difficult.



Scheme 137: Attempts at RCM utilizing crude 441

Having previously shown that mono deprotection of the amine functionality and selective ester reduction of amino ester **330** could be achieved, it was decided to concentrate upon the formal synthesis of furanomycin, up to immediate **421** as reported by Standaert *et al.*[152] First **436** was subjected to two equivalents of TFA in DCM at 0 °C for 4 hours afforded **442** in 79% yield. Although a longer reaction time was required, none of the free amine was observed. Subsquently **442** was treated with two equivalents of lithium aluminum hydride to reduce the amino ester to amino alcohol **421** in 65% yeild. Therefore a formal synthesis of furanomycin was completed, starting from (*S*)-butyn-2-ol **(*S*)-189** to *N*-Boc furanomycinol **421**, in 4.9% yield over 8 steps.



Scheme 138: Formal synthesis of *N*-Boc Furanomycinol 421

4.3 CONCLUSIONS

Access to the *anti*-diastereomer has been shown to be limited. The SKA investigations show that the (*Z*)-SKA is the major geometry formed, therefore the use of HMPA to change the SKA geometry would not have been applicable. Instead, switching to a (*Z*)-allylic enol ether, led to the *anti*-diastereomer, however limited diastereoselectivity was observed.

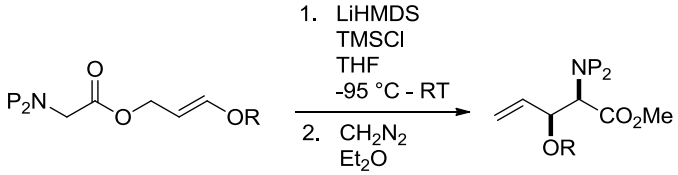
Key transformations such as amine deprotection can be selectively achieved utilizing the *N*-Diboc products, along with the removal of protecting groups sensitive to hydrogenolysis (such as 2-methyl benzyl) has also been shown. Saponification of the methyl ester has however proved more difficult due to the sensitivity of these compounds towards alkali bases and other protocols such as utilizing potassium trimethylsilanote have also proved ineffective. Further functionalisation of the resultant alkene has been explored utilizing RCM methodology, resulting in the formation of the main core of norfuranomycin **387** and a key intermediate for the synthesis of iminosugars.

Finally, several of these transformations have been incorporated into a formal synthesis of furanomycin starting from (*S*)-butyn-2-ol, in 4.9% in 8 steps.

CHAPTER 5 CONCLUSIONS AND FUTURE WORK

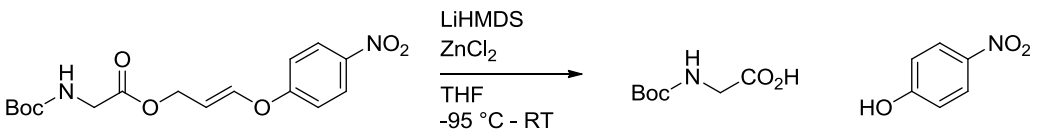
5.1 CONCLUSIONS

A new synthetic approach to β-hydroxy α-amino acids has been established utilizing the Ireland-Claisen rearrangement of allylic amino esters generated, from an amino acid and an allylic enol ether (Scheme 139).



Scheme 139: Ireland-Claisen rearrangement of allylic amino esters to β-hydroxy α-amino acids

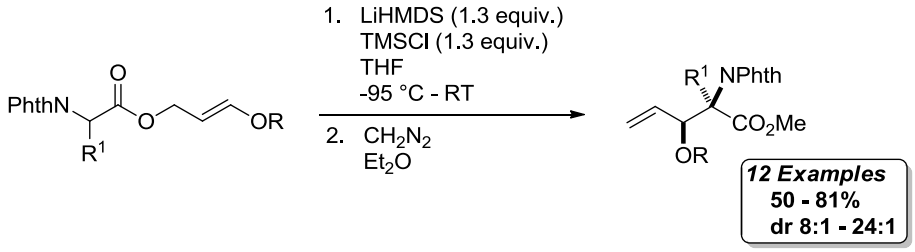
The development of this methodology initially centred on utilizing the protocol developed by Kazmaier of metal chelated enolates. However, none of the desired rearranged product was obtained; instead decomposition back to the starting components was observed (Scheme 140). This has been postulated to occur due to the significant dipolar character of the transition state.



Scheme 140: Decomposition utilizing Kazmaier's protocol

Switching to a more traditional Ireland-Claisen type protocol utilizing *N*-Phthaloyl glycine, successfully allowed for a *syn*-selective rearrangement, with a wide scope of ethereal groups tolerated producing good yields and diastereoselectivities (Scheme 141). The rearrangement has been observed to be sensitive to a wide range of variables such as initiation temperature and base addition rate. One limitation to the use of a phthalimde protecting group is that only allylic enol ethers containing primary or phenoxy based ethereal groups can be successfully coupled to form the required allylic amino ester. The rearrangement of an allylic amino ester derived from *rac*-alanine was also accomplished with high levels of *syn*-selectivity. This opens up a general diastereoselective route into synthesizing serine/alanine adducts or further α,α-

substituted hybrid amino acid fragments resembling the β-hydroxy α-amino acid seen in several natural products such as sphingofungin F.

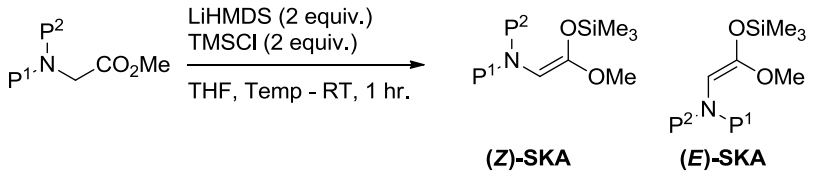


Scheme 141: Successful rearrangement using a phthalimde protected nitrogen under traditional Ireland-Claisen rearrangement conditions

Switching the study from the ethereal oxygen, *N*-substitution using several commonly used protecting groups was investigated. A range of amino acids were synthesised and investigated with all but one displaying little to no selectivity. *N*-Diboc glycine was observed to rearrange in a *syn*-selective fashion to afford the desired β-alkoxy α-amino ester products as single diastereomers. Importantly, this was also observed to be applicable to allylic amino esters containing secondary ethereal oxygens.

Due to a large variation in selectivity being observed an investigation into the formation of the SKA was invoked. This provided a large insight into the relative formation of SKA geometries through to the diastereoselectivity and mechanism of the rearrangement. With three amino esters investigated, the ratio of *E*/*Z* geometries of the SKAs formed showed a direct correlation with the diastereoselectivity obtained utilizing the methoxy enol ether substrate (Table 24).

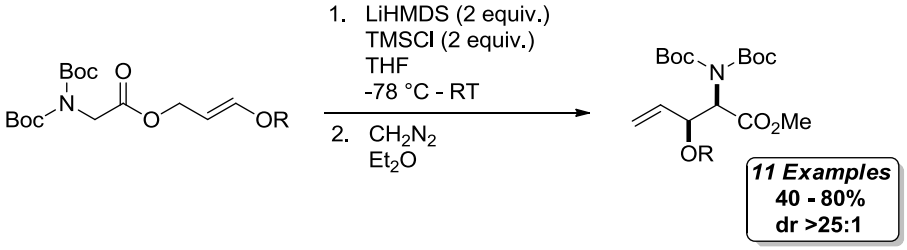
Table 24: SKA investigation



232 $P^1 = P^2$ = Phth
335 $P^1 = P^2$ = Boc
336 P^1 = Boc, P^2 = Me

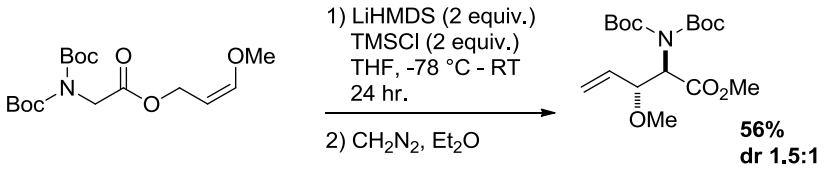
Entry	Substrate	Temp (°C)	SKA/SM	Yield SKA (%)	*Z*/*E*	Rearrangement dr (OMe, *syn*:*anti*)
1	**232**	-95	7:1	87	12:1	11:1
2	**335**	-78	1.4:1	51	>25:1	>25:1
3	**336**	-95	4:1	81	2:1	2:1

The scope of the rearrangement was once again investigated using the *N*-diboc glycine as the amino acid coupling partner. Again a large range of ethereal functional groups were tolerated, rearranging in good yield as a single diastereomer (Scheme 142). Also important to note is the selectivity achieved when rearranging allylic amino esters containing a chiral centre.



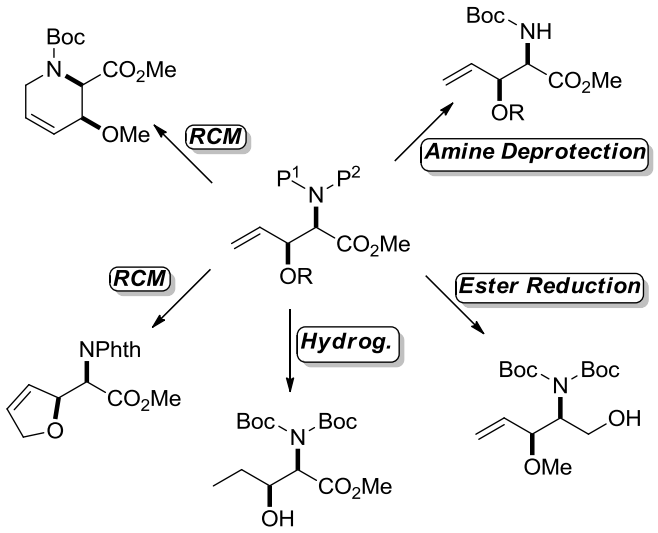
Scheme 142: Successful rearrangement using *N*-Diboc glycine affording β-hydroxy α-amino acids as a single diastereomer

Access to the *anti*-diastereomer has been shown to be limited. The SKA investigations show that the (*Z*)-SKA is the major geometry formed, therefore the use of HMPA to change the SKA geometry would not have been applicable. Instead, switching to a (*Z*)-allylic enol ether, led to the *anti*-diastereomer, however limited diastereoselectivity was observed (Scheme 143).



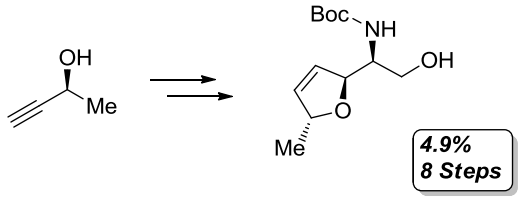
Scheme 143: Limited access to the anti-diastereomer

Key transformations such as amine deprotection can be selectively achieved utilizing the *N*-diboc products, whilst removal of protecting groups sensitive to hydrolysis has also been shown. Saponification of the methyl ester has however proved more difficult due to the sensitivity of these compounds towards alkali bases. Further functionalisation of the resultant alkene has been expored utilizing RCM methodology, resulting in the formation of the main core of norfuranomycin and a key intermediate for the synthesis of iminosugars being achieved (Scheme 144).



Scheme 144: Several functionalisations of the β-alkoxy α-amino esters

Finally, several of these transformations have been incorporated into a formal synthesis of furanomycin starting from (*S*)-butyn-2-ol, in 4.9% in 8 steps (Scheme 145).

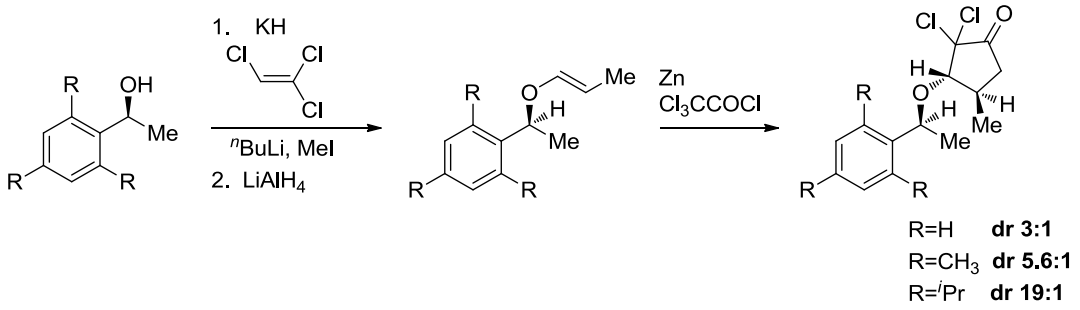


Scheme 145: Synthesis of *N*-Boc furanomycinol

5.2 FUTURE WORK

5.2.1 *Chiral enol ethers*

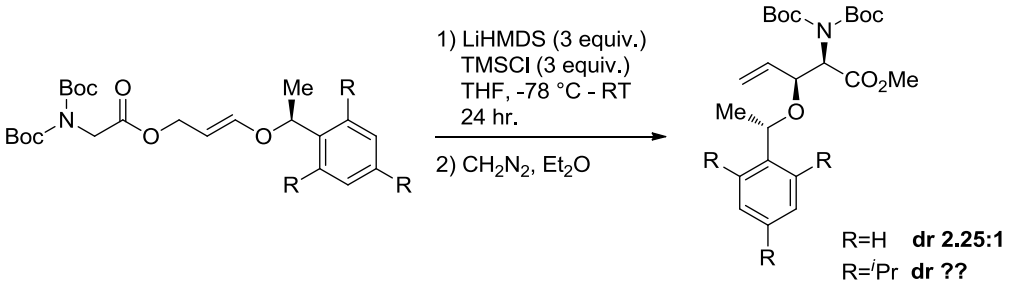
Greene *et al.* have reported the use of chiral enol ethers in an asymmetric [2+2] cycloaddition for the synthesis of β-oxygenated lactones.[141] When starting from (*S*)-1-phenylethanol (R=H**)** the β-benzyloxy cyclopentanone was obtained in a diastereoselectivity of 3:1 (Scheme 146).



Scheme 146: Greene's observations of increasing diastereoselctive control with increasing steric benzyl enol ether

They observed greater π-facial selectivity was achieved and hence improved diastereoselective control when utilizing substitued benzyl chiral enol ethers.

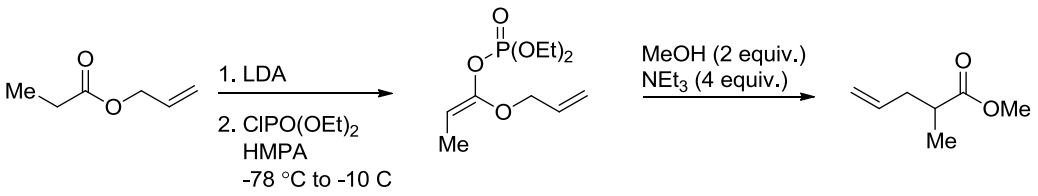
Utilzing this observation, increasing the steric bulk upon chiral benzylic allylic enol ethers to substituents such as isopropyl groups could might allow the rearrangement to proceed in a completly diastereoselective manner (Scheme 147).



Scheme 147: Chiral benzylic enol ether rearrangement

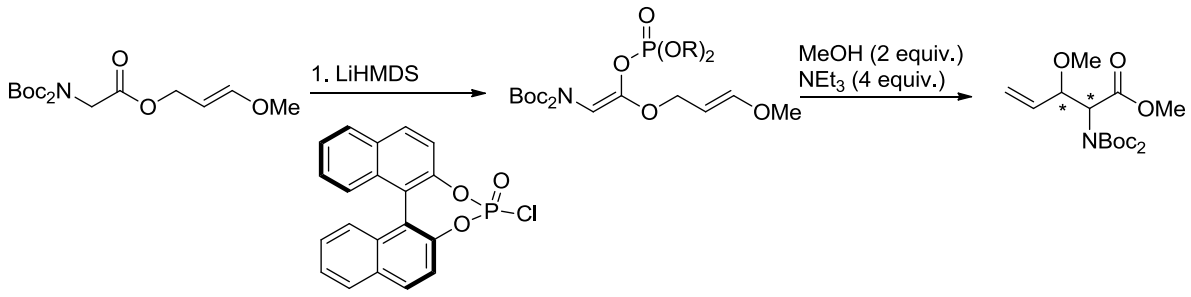
5.2.2 *Chiral phosphates*

Funk has previously reported the rearrangement of enol phosphates (Scheme 148).[160]



Scheme 148: Funk's enol phosphate rearrangement

Utilizing Funk's procedure, substituting the diethyl phosphorochloridate for a chiral variant (Scheme 149), should lead to a diastereo- and enantioselective rearrangement of our allylic amino ester substrate.

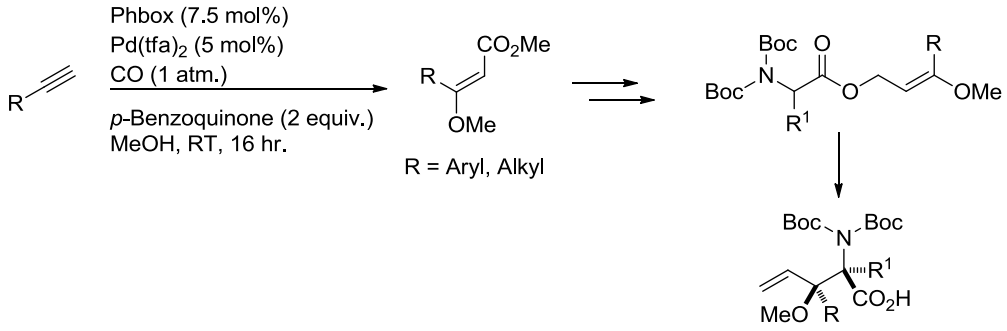


Scheme 149: Possible use of chiral phosphorochloride to induce absolute chirality within our rearrangement

Although our substrate has been shown to be sensitive to HMPA, initial investigation with other solvents could allow for a successful rearrangement and therefore proof of concept can be obtained.

5.2.3 *Alkene substitution*

Several natural products containing β-hydroxy α-amino acids moieties contain contiguous stereocentres. Utilizing substitution on the alkene unit coupled with substituted amino acids, will lead to the generation of two new stereocentres. More so, Kato *et al.* have recently reported the synthesis of β-methoxyacrylates starting from terminal acetylenes. Utilizing his methodology to synthese β-methoxyacrylates would allow for the synthesis of the allylic amino esters *via* the already optimised route (Scheme 150).[161]

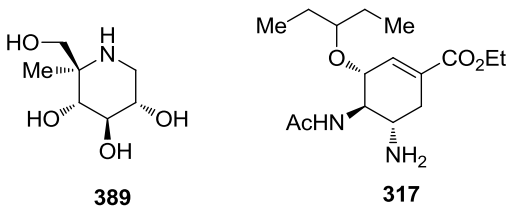


Scheme 150: Kato synthesis of β-methoxyacrylates leading to contiguous stereocentres after rearrangement of the allylic amino ester.

5.2.4 *Natural product synthesis*

Primary investigation into natural product synthesis should concentrate upon improving and completing the synthesis of furanomycin. First, since protection of the carboxylic acid functionality is required after rearrangement to allow for flash chromatographic purification, protection as either a *tert*-butyl ester or *p*-methoxybenzyl ester should allow for a global deprotection, therefore also reducing the number of steps in the synthesis. Also improvement of the rearrangement diastereoselectivity, to afford the desired amino ester as a single diastereomer would considerably improve the synthesis. Changing the substitution of the ethereal fragment however is very limited. Since the addition of the bulk phenyl ring not only yielded similar diastereoselectivities, but also impeded the RCM. Alternatives would see a large group at this position instead of the methyl group, however, further manipulation of this group is required to yield a methyl group for the final compound.

Several more natural products can be synthesized *via* this methodology. More importantly the key substrates and rearrangements have already been investigated and have been shown to proceed successfully to the required intermediates for the synthesis of both these compounds (Figure 36).



389 **317**

Figure 36: Two further natural product targets: 1-deoxymojorimycin 389 and oseltamivir 317.

CHAPTER 6 EXPERIMENTAL

6.1 GENERAL EXPERIMENTAL

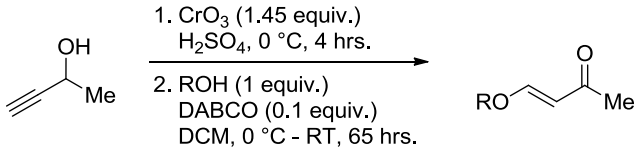
Reactions were carried out using anhydrous solvents and under an inert atmosphere of nitrogen. All reaction vessels were flame dried prior to use. Anhydrous acetonitrile, diethyl ether, dichloromethane, hexane, toluene and tetrahydrofuran were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. All other commercially available compounds were used as obtained from the chemical suppliers and used without purification. Triethylamine and methyl *trans*-3-methoxyacrylate were freshly distilled, diisopropylamine was freshly distilled from sodium hydroxide pellets and chlorotrimethylsilane was freshly distilled from 10 % quinoline. Zinc chloride was dried at 130 °C and 1.2 torr for 90 minutes prior to use. Diazomethane was generated by the addition of potassium hydroxide solution (37%) to *N*-nitroso-*N*-methylurea in ether. All distilled materials were stored under nitrogen at 4 ^{o}C or less. All reactions were monitored by thin layer chromatography (TLC) using pre-coated MN Alugram Sil G/UV254 silica gel 60 aluminium backed plates. Plates were developed using standard techniques, UV light (at 254 nm) followed by a chemical dip, usually $KMnO_4$ and gentle heating. Flash chromatography was performed on chromatography grade, silica 60Å particle size 35-70 micron from Fisher Scientific or chromatography grade basic Brockmann I grade alumina particle size 50 – 200 micron from Acros Organics using the solvent system as stated. Samples were pre-absorbed onto silica/alumina or loaded as saturated solutions in an appropriate solvent. Ether refers to diethyl ether and petrol refers to the fraction of petroleum ether boiling at 40-60 °C.

^{1}H and ^{13}C NMR was performed on Brüker Avance 250 (^{1}H 250 MHz), Brüker Avance 300 (^{1}H 300 MHz and ^{13}C 75 MHz), Brüker Avance 400 (^{1}H 400 MHz and ^{13}C 100 MHz) and Brüker Avance 500 (^{1}H 500 MHz and ^{13}C 125 MHz) as stated. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) (δ □= 0.00). Coupling constants are reported in Hertz (Hz) and signal multiplicity as denoted. Rotamers were confirmed by variable temperature (VT) ^{1}H NMR and ratios determined at room temperature using either Brüker Avance 400 (^{1}H 400 MHz and ^{13}C 100 MHz) or Brüker Avance 500 (^{1}H 500 MHz and ^{13}C 125 MHz) as stated. Where rearranged products are obtained as a diastereomeric and rotameric mixture,data reported

corresponds to both sets of rotamers for the major diastereomer only, regardless of ratio. Mass spectroscopy was performed on a a Brüker Daltonics micrOTOF using electrospray ionisation (ESI) in either positive or negative ionization as stated. Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling. Melting points were determined using a Bibby Scientific Melting point apparatus Stuart SMP10 digital and are reported as uncorrected. X-ray data was collected at 150 K on a Nonius KappaCCD area detector diffractometer using Mo-Kα radiation (λ = 0.71073 Å), and all structures were solved by direct methods and refined on all *F2* data using SHELXL-97 suite of programs, with hydrogen atoms included in idealized positions and refined using the riding model.

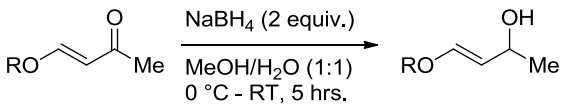
6.2 GENERAL PROCEDURES

General Procedure 1 Synthesis of 4-aryloxy but-3-en-2-ones



To a stirred solution of chromium (VI) oxide (4.00 g, 40 mmol, 1.45 equiv.) in H_2SO_4 (20% v/v, 150 mL) was added 3-butyn-2-ol (2.2 mL, 27.5 mmol, 1 equiv.) in H_2SO_4 (20% v/v, 150 mL) at 0 °C and stirred for 4 hours. The reaction was extracted with DCM (3 × 100 mL). The combined organics were washed with 1:1 saturated bicarb/water solution (3 × 100 mL), dried over Na_2SO_4 and filtered. The crude ketone was added dropwise over 1 hour to a solution of an alcohol (1 equiv.) and DABCO (0.31 g, 2.75 mmol, 0.1 equiv.) in DCM (10 mL) at 0 °C, warmed to room temperature and stirred for a further 64 hours. The resulting solution was concentrated *in vacuo* to c.a. 100 mL, washed with water (3 × 75 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound.

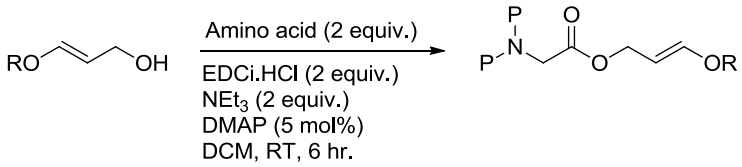
General Procedure 2 Synthesis of 4-aryloxy but-3-en-2-ols



To a stirred to solution of 4-aryloxy but-3-en-2-one (2.35 g, 11.4 mmol, 1 equiv) in methanol and water (1:1, 10 mL) at 0 °C was added sodium borohydride (0.91 g, 22.8 mmol, 2 equiv.) portionwise. The resultant suspension was stirred at room temperature for 5 hours before extracting with DCM (3 × 25 mL). The organic fractions were

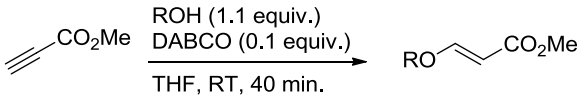
combined and washed with saturated bicarbonate solution (3 × 50 mL) and brine (3 × 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound.

General Procedure 3 Synthesis of amino esters substrates



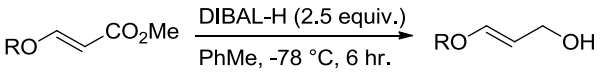
To a stirred solution of EDCi.HCl (2 equiv.) in DCM (50 mL) was added triethylamine (2 equiv.), amino acid (2 equiv.), catalytic DMAP (5 mol %) and allylic alcohol (1 equiv.). The reaction is stirred at room temperature for 4 hours or until consumption of allylic alcohol is complete by TLC. Dilution with DCM to 100 mL, followed by washing with saturated sodium bicarbonate solution (3 × 100 mL), citric acid (10% solution, 3 × 100 mL) and brine (3 × 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford amino esters without any further purification, unless stated.

General Procedure 4 Synthesis of vinylogous esters



To a stirred solution of 1,4-diazabicyclo[2.2.2]octane (0.1 equiv.) and alcohol (1.1 equiv.) in THF (150 mL) at room temperature was added methyl propiolate (1 equiv.) *via* syringe pump over 10 minutes, before stirring at room temperature for a further 30 minutes. Sodium hydroxide (10% solution, 200 mL) was added and the aqueous was extracted with DCM (4 × 100 mL), combined, washed with brine (3 × 150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product ester was isolated after subsequent purification on silica gel by flash chromatography.

General Procedure 5 Synthesis of allylic alcohols

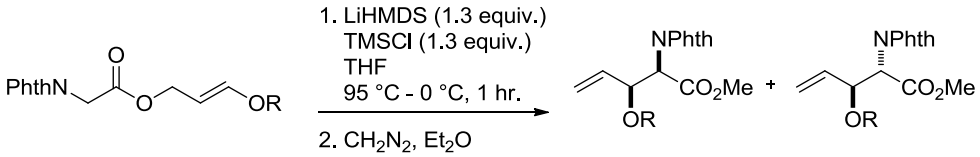


To a stirred solution of the ester (1 equiv.) in toluene (100 mL) at -78 °C was added diisobutylaluminium hydride solution (1M in toluene, 2.5 equiv.) at a rate of 1 mL min^{-1}. After addition the reaction was stirred at -78 °C for 6 hours, before pouring onto

a Rochelle's salt solution (sat., 100 mL) followed by the addition of EtOAc (100 mL). The biphasic mixture was vigorously stirred for 2 hours before separating and extracting with EtOAc (3 × 100 mL). The organics were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the primary allylic alcohol product without further purification, unless stated.

General Procedure *6* ***Ireland-Claisen rearrangements***

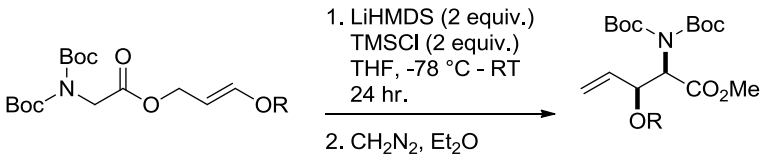
– Phthamide protected substrates



To a stirred solution of the amino ester (1 equiv.) in THF (1 mL) at -95 °C is added TMSCl (1.3 equiv.) and stirred for 10 minutes. LiHMDS (1M in THF, 1.3 equiv.) was added *via* syringe pump at a rate of 3 mL hr^{-1} and the mixture stirred at -95 °C for a further 10 minutes before warming to 0 °C and stirring for 30 minutes. The reaction is quenched by the addition of 1M HCl and brine solution (1:1, 2 mL). The reaction mixture is extracted with DCM (3 × 10 mL) and ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude acid. Treatment with excess diazomethane (generated from NMU in situ) in ether afforded the methyl ester. Purification was achieved by flash chromatography to afford the title compound as an inseparable mixture of diastereomers.

General Procedure *7* ***Ireland-Claisen rearrangements***

– Di-boc protected substrates

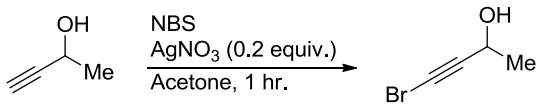


To a stirred solution of the amino ester (1 equiv.) in THF (1 mL) at -78 °C is added TMSCl (2 equiv.) and stirred for 10 minutes. LiHMDS (1M in THF, 2 equiv.) was added *via* syringe pump at a rate of 3 mL hr^{-1} and the mixture stirred at -78 °C for a further 10 minutes before warming to room temperature and stirring for 24 hours. The reaction is quenched by the addition of methanol (10 mL). Treatment with excess diazomethane (generated from NMU in situ) in ether afforded the methyl ester.

Purification was achieved by flash chromatography to afford the title compound as a single diastereomer.

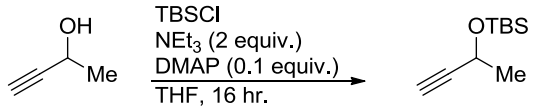
6.3 COMPOUND CHARATERISATION

4-Bromo-3-butyn-2-ol (190)



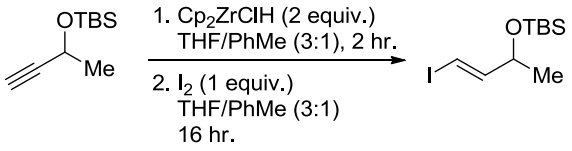
To a stirred solution of *N*-bromosuccinimide (5.07 g, 28.5 mmol, 1 equiv.) and silver nitrate (1.00 g, 5.9 mmol, 0.2 equiv.) in acetone (30 mL) was added 3-butyn-2-ol **189** (2.24 mL, 28.5 mmol, 1 equiv.). After 1 hour, the reaction mixture was concentrated *in vacuo* to approximately 10 mL, filtered through a pad of silica and washed through with DCM (50 mL). The solution was then concentrated *in vacuo* to afford the title compound as a yellow oil and used without any further purification (3.30 g, 75%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.39 (d, 3H, *J* = 6.6 Hz, BrC≡CCH(OH)C*H*$_3$), 3.51 (br s, 1H, BrC≡CCH(O*H*)CH$_3$), 4.48 (q, 1H, *J* = 6.6 Hz, BrC≡CC*H*(OH)CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.1, 42.1, 58.8, 81.3. All analytical data is in accordance with commercial sources.

(But-3-yn-2-yloxy)(*tert*-butyl)dimethylsilane (192)



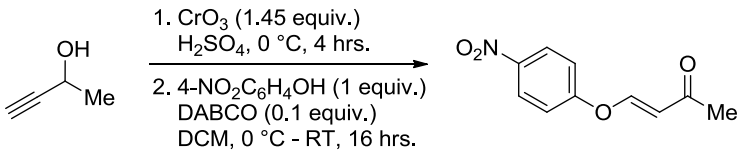
To a stirred solution of 3-butyn-2-ol **189** (5.60 mL, 71.3 mmol, 1 equiv.) in THF (50 mL) was added DMAP (0.81 g, 7.1 mmol, 0.1 equiv.), triethylamine (19.8 mL, 143 mmol, 2 equiv.) and *tert*-butylchlorodimethylsilane (10.75 g, 71.3 mmol, 1 equiv.). The solution was stirred for 16 hours at room temperature, filtered through a pad of silica and washed through with THF (50 mL) and concentrated *in vacuo*. The crude product was taken up in DCM (100 mL) and filtered through a second pad of silica and concentrated *in vacuo* to afford the title compound as a yellow oil and used without any further purification (8.36 g, 64%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.08 (s, 3H, Si(C*H*$_3$)$_2$(C(CH$_3$)$_3$), 0.12 (s, 3H, Si(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.90 (s, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 1.44 (d, 3H, *J* = 6.6 Hz, CCH(OSi)C*H*$_3$), 2.38 (d, 1H, *J* = 2.0 Hz, *H*C≡CCH(OSi)CH$_3$), 4.52 (qd, 1H, *J* = 6.6, 2.0 Hz, HC≡CC*H*(OSi)CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: -4.3, -3.2, 18.3, 25.2, 25.6, 58.8, 70.9, 86.3. All analytical data is in accordance with reported literature values.[162]

(*E*)-*tert*-Butyl(4-iodo-3-en-2-yloxy)dimethysilane (193)



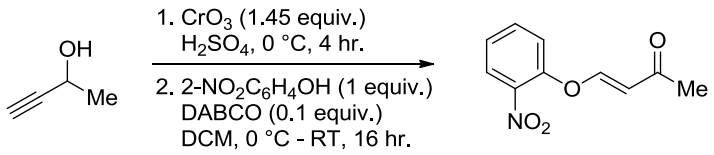
To a stirred solution of bis(cyclopentadienyl)zirconium(IV) hydrochloride (0.26 g, 1 mmol, 1 equiv.) in toluene (5 mL) was added (but-3-yn-2-yloxy)(*tert*-butyl)dimethylsilane **192** (0.18 g, 1 mmol, 1 equiv.) in THF (15 mL). After 15 minutes a further portion of *bis*(cyclopentadienyl)zirconium(IV) hydrochloride (0.26 g, 1 mmol, 1 equiv.) in toluene/THF (3:1, 20 mL) was added. After a further 2 hours, iodine (0.25 g, 1 mmol, 1 equiv.) was added before stirring for 16 hours. The mixture was diluted with hexane (25 mL), filtered through a pad of silica and concentrated *in vacuo* to afford the title compound as a yellow oil (0.08 g, 25%). FTIR (film/cm^{-1}) υ_{max}: 3012.5, 2958.3, 1659.7; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.00 (m, 6H, $Si(CH_3)_2C(CH_3)_3$), 0.84 (s, 9H, $Si(CH_3)_2C(CH_3)_3$), 1.15 (d, 3H, *J* = 6.6 Hz, $CHCH(OSi)CH_3$), 4.21 (qt, 1H, *J* = 6.6, 1.2 Hz, $ICH=CHCH(OSi)CH_3$), 6.17 (app. dd, 1H, *J* = 13.7, 1.2 Hz, $ICH=CHCH(OSi)CH_3$), 6.49 (dd, 1H, *J* = 13.7, 1.2 Hz, $ICH=CHCH(OSi)CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: -4.3, -3.2, 18.4, 25.3, 25.8, 71.1, 97.5, 150.1.

(*E*)-4-(4-Nitrophenoxy)but-3-en-2-one (205)



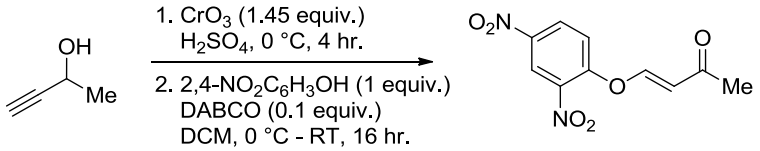
According to general procedure 1, the title compound was synthesised using 4-nitrophenol (3.83 g, 27.5 mmol, 1 equiv.). Purification was achieved by recrystalisation from hot methanol, affording the title compound as pale yellow crystals (3.00 g, 53%). MP: 70 – 71 °C; FTIR (nujol mull/cm^{-1}) υ_{max}: 3088.3, 1702.8, 1643.7; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.22 (s, 3H, $=CHCOCH_3$), 6.10 (d, 1H, *J* = 10.2 Hz, $ArOCH=CHCOCH_3$), 7.16 (dt, 2H, *J* = 9.2, 3.3 Hz, Ar-*H* Ph), 7.70 (d, 1H, *J* = 10.2 Hz, $ArOCH=CHCOCH_3$), 8.25 (dt, 2H, *J* = 9.2, 3.3 Hz, Ar-*H* Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.1, 113.8, 117.8, 126.1, 144.5, 155.5, 160.2, 196.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_{10}H_{10}NO_4$ 208.0610, found 208.0617 $(M+H)^+$.

(*E*)-4-(2-Nitrophenoxy)but-3-en-2-one (206)



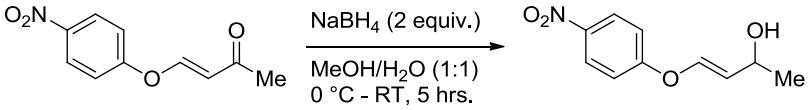
According to general procedure 1, the title compound was synthesised using 2-nitrophenol (3.83 g, 27.5 mmol, 1 equiv.). Purification was achieved by recrystalisation from hot methanol, affording the title compound as pale yellow crystals (2.53 g, 40%). MP: 65 – 67 °C; FTIR (nujol mull/cm^{-1}) υ_{max}: 3085.7, 1647.3; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.17 (s, 3H, =CHCOC*H*$_3$), 5.83 (d, 1H, *J* = 12.4 Hz, ArOCH=C*H*COCH$_3$), 7.25 (m, 2H, Ar-*H* Ph), 7.59 (dt, 2H, *J* = 7.9, 2.1 Hz, Ar-*H* Ph), 7.91 (d, 1H, *J* = 12.4 Hz, ArOC*H*=CHCOCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.1, 113.3, 126.2, 126.4, 139.8, 141.6, 148.6, 150.8, 158.2, 197.0; HRMS (ESI, +ve) *m/z*: calcd. for $C_{10}H_{10}NO_4$ 208.0610, found 208.0612 $(M+H)^+$.

(*E*)-4-(2,4-Dinitrophenoxy)but-3-en-2-one (207)



According to general procedure 1, the title compound was synthesised using 2,4-dinitrophenol (5.06 g, 27.5 mmol, 1 equiv.). The crude compound was recrystalised from hot methanol, affording the title compound as pale yellow crystals (4.57 g, 66%). MP: 70 – 72 °C; FTIR (nujol mull/cm^{-1}) υ_{max}: 3055.7, 1667.3; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.22 (s, 3H, =CHCOC*H*$_3$), 6.12 (d, 1H, *J* = 12.2 Hz, ArOCH=C*H*COCH$_3$), 7.44 (m, 3H, Ar-*H* Ph), 7.64 (d, 1H, *J* = 12.2 Hz, ArOC*H*=CHCOCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.1, 112.8, 117.2, 128.8, 139.5, 142.4, 145.9, 148.0, 154.0, 197.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_{10}H_9N_2O_6$ 253.0461, found 253.0449 $(M+H)^+$.

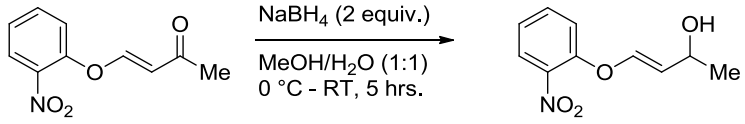
(*E*)-4-(4-Nitrophenoxy)but-3-en-2-ol (208)



According to general procedure 2, the title compound was synthesised using (*E*)-4-(4-nitrophenoxy)but-3-en-2-one **205**. Purification was achieved by recrystalisation from chloroform/petrol, affording the title compound as pale white powder (1.85 g, 77%).

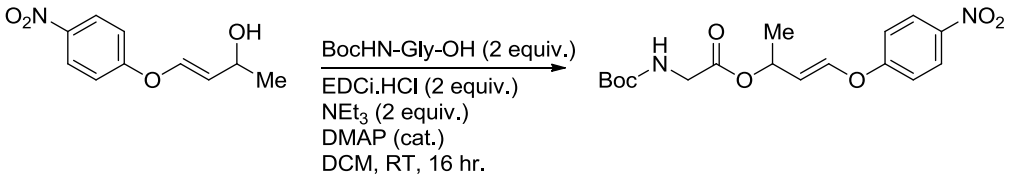
MP: 78 – 80 °C; FTIR (nujol mull/cm^{-1}) υ_{max}: 3305.4; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.31 (d, 3H, *J* = 6.3 Hz, =CH(OH)C*H*$_3$), 1.62 (br, 1H, =CH(O*H*)CH_3), 4.40 (quin, 1H, *J* = 6.3 Hz, =C*H*(OH)CH_3), 5.56 (dd, 1H, *J* = 12.0 Hz, OCH=C*H*CH(OH)CH_3), 6.65 (d, 1H, *J* = 12.0 Hz, OC*H*=CHCH(OH)CH_3), 7.02 (m, 2H, Ar-*H* Ph), 8.18 (m, 2H, Ar-*H* Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.6, 65.8, 116.6, 120.6, 126.4, 141.5, 143.3, 162.1; HRMS (ESI, -ve) *m/z*: calcd. for $C_{10}H_{10}NO_4$ 208.1907, found 208.1610 (M-H).

(*E*)-4-(2-Nitrophenoxy)but-3-en-2-ol (209)



According to general procedure 2, the title compound was synthesised using (*E*)-4-(2-nitrophenoxy)but-3-en-2-one **206**. Purification was achieved by recrystalisation from chloroform/petrol, affording the title compound as pale white powder (1.65 g, 70%). MP: 80 – 81 °C; FTIR (nujol mull/cm^{-1}) υ_{max}: 3310.6; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.39 (d, 1H, *J* = 6.3 Hz, OCH=CHCH(OH)C*H*$_3$)), 1.54 (br, 1H, OCH=CH(O*H*)CH_3), 4.47 (quin, 1H, *J* = 6.3 Hz, OCH=CHC*H*(OH)CH_3), 5.58 (dd, 1H, *J* = 12.8, 6.3 Hz, OCH=C*H*CH(OH)C*H*$_3$)), 6.70 (d, 1H, *J* = 12.8 Hz, OC*H*=CHCH(OH)C*H*$_3$)), 7.18 – 7.95 (m, 4H, Ar-*H* Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6, 64.6, 112.2, 119.7, 123.8, 127.6, 135.5, 136.3, 139.8, 142.0; HRMS (ESI, -ve) *m/z*: calcd. for $C_{10}H_{10}NO_4$ 208.1907, found 208.1923 (M-H).

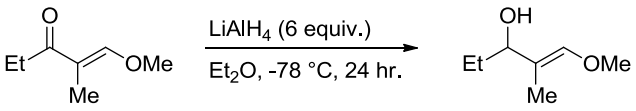
(*E*)-4-(4-Nitrophenoxy)but-3-en-2-yl 2-((*tert*-butoxycabonyl)(methyl)anino)acetate (210)



EDCi.HCl (1.33 g, 7.00 mmol), triethylamine (1.00 mL, 7.00 mmol), *N*-boc glycine (1.22 g, 7.00 mmol), catalytic DMAP and (*E*)-4-(4-nitrophenoxy)but-3-en-2-ol **208** (0.74 g, 3.50 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (0.90 g, 70%). FTIR (nujol mull/cm^{-1}) υ_{max}: 3010.7, 2980.3, 1757.6, 1718.0, 1671.7; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.35 – 1.40 (m, 12H, (C*H*$_3$)$_3$COCON & OCH(C*H*$_3$)CH=CHO), 3.83 (d, 2H, *J* = 5.8 Hz, NC*H*$_2$CO$_2$), 4.94 (br, 1H, N*H*), 5.38 – 5.49 (m, 2H, OCH(CH_3)C*H*=CHO & OC*H*(CH_3)CH=CHO), 6.78 (dt,

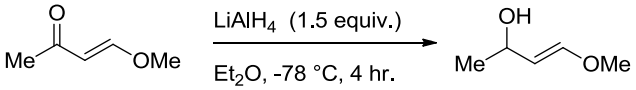
1H, *J* = 11.7, 4.9 Hz, OCH(CH_3)CH=C*H*O), 6.98 – 7.04 (m, 2H, Ar-H Ph), 8.13 - 8.20 (m, 2H, Ar-*H* Ph);[13]C NMR (75 MHz, $CDCl_3$) δ: 21.1, 28.7, 43.1, 69.3, 80.3, 115.2, 116.8, 126.3, 143.5, 144.6, 156.2, 161.7, 170.2; HRMS (ESI, -ve) *m/z*: calcd. for $C_{17}H_{21}N_2O_7Na$ 365.1354, found 365.1435 (M-H).

(*E*)-1-Methoxy-2-methylpent-1-en-3-ol (220)



To a stirred solution of lithium aluminium hydride (0.91 g, 24 mmol, 6 equiv.) in ether (5 mL) was added (1*E*)-1-methoxy-2-methyl-1-penten-3-one **219** (0.53 mL, 4 mmol, 1 equiv.) dropwise at -78 °C and stirred for 8 hours. The mixture was warmed room temperature and stirred for a further 16 hours before quenching with water (0.9 mL), sodium hydroxide (15%, 0.9 mL) and further water (2.7 mL). The slurry was filtered through a pad of celite and concentrated *in vacuo* to afford the title compound as a colourless oil and used without further purification (0.22 g, 60%). FTIR (film/cm^{-1}) υ_{max}: 3442.9; [1]H NMR (250 MHz, $CDCl_3$) δ: 0.85 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$CH(OH)), 1.58 (m, 5H, CH_3CH_2CH(OH) & EtCH(OH)C(C*H*$_3$)C=CH), 3.60 (s, 3H, OC*H*$_3$), 3.83 (td, 1H, *J* = 7.0, 3.1 Hz, CH_3CH_2C*H*(OH)C), 6.02 (s, 1H, C=C*H*OCH$_3$); [13]C NMR (75 MHz, $CDCl_3$) δ: 8.1, 10.6, 27.9, 59.9, 76.1, 77.0, 145.2.

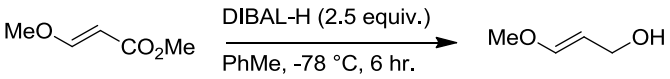
(*E*)-4-Methoxybut-3-en-2-ol (222)



To a stirred solution of lithium aluminium hydride (0.57 g, 15 mmol, 1.5 equiv.) in ether (200 mL) at -78 °C was added a solution of (*E*)-4-methoxy-3-buten-2-one **221** (1.00 g, 10 mmol, 1 equiv.) in ether (10 mL) *via* syringe pump. The mixture was stirred at -78 °C for 4 hours, before diluting with ether and quenching with ethyl acetate, followed by stirring with saturated Rochelle salt solution for 2 hours. The mixture was extracted with EtOAc (2 × 50 mL) dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (0.82 g 80%). FTIR (film/cm^{-1}) υ_{max}: 3367.0, 2970.1, 2932.1, 2835.0, 1652.8; [1]H NMR (500 MHz, d_6-acetone) δ: 1.19 (d, 3H, *J* = 6.4 Hz, C*H*$_3$CH(OH)), 3.48 (s, 3H, OC*H*$_3$), 4.17 – 4.23 (m, 1H, CH_3C*H*(OH)), 4.83 (dd, 1H, *J* = 12.7, 5.2 Hz, CH_3CH(OH)C*H*=CHOCH$_3$), 6.50 (d, 1H,

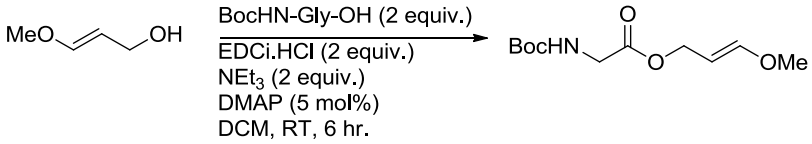
J = 12.7 Hz, $CH_3CH(OH)CH=CHOCH_3$); ^{13}C NMR (125 MHz, d_6-acetone) δ: 24.4, 55.0, 65.2, 108.4, 147.8.

(*E*)-3-(Methoxy)prop-2-enol (224)



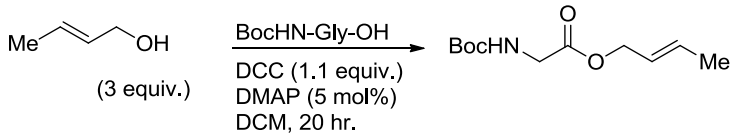
(*E*)-Methyl 3-(methoxy)acrylate **223** (2.00 g, 17.2 mmol) was reduced according to general procedure 5 to afford the product as a yellow oil (1.17 g, 77%). FTIR (film/cm^{-1}) υ_{max}: 3354.8, 2957, 2873.9, 1657.1; ^1H NMR (500 MHz, d_6-acetone) δ: 3.35 (t, 1H, *J* = 5.7 Hz, $CH_3OCH=CHCH_2OH$), 3.51 (s, 3H, CH_3O), 3.96 (t, 2H, *J* = 7.0 Hz, $CH_3OCH=CHCH_2OH$) 4.96 (dt, 1H, *J* = 12.7, 7.0 Hz, $CH_3OCH=CHCH_2OH$), 6.51 (d, 1H, *J* = 12.7 Hz, $CH_3OCH=CHCH_2OH$); ^{13}C NMR (125 MHz, d_6-acetone) δ: 55.1, 59.1, 102.9, 149.5. All analytical data is in accordance with reported literature values.[124]

(*E*)-3-Methoxyallyl 2-((*tert*-butoxycarbonyl)amino)acetate (180)



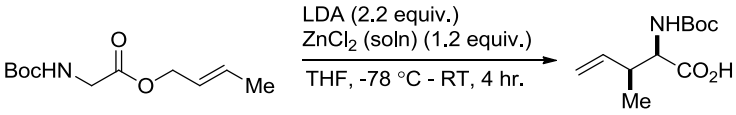
EDCi.HCl (2.50 g, 17.0 mmol), triethylamine (1.6 mL, 17.0 mmol), *N*-Boc-Gly-OH **184** (2.24 g, 17.0 mmol) and (*E*)-3-(methoxy)prop-2-enol **224** (0.75 g, 8.51 mmol) were combined according to general procedure 3, to afford the title compound as a colourless oil (1.45 g, 70%). FTIR (film/cm^{-1}) υ_{max}: 2880.3, 1736.1, 1717.6, 1673.9; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.38 (s, 9H, $(CH_3)_3COCON$), 3.51 (s, 3H, $OCH_2CH=CHOCH_3$), 3.83 (app. q, 2H, *J* = 5.6 Hz, NCH_2CO_2), 4.51 (d, 2H, *J* = 7.8 Hz, $OCH_2CH=CHOCH_3$), 4.89 (dt, 1H, *J* = 12.7, 7.8 Hz, $OCH_2CH=CHOCH_3$), 4.99 (br, 1H, NH), 6.59 (d, 1H, *J* = 12.7 Hz, $OCH_2CH=CHOCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4, 42.7, 55.1, 66.3, 80.2, 125.9, 136.7, 156.0, 171.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{11}H_{19}NO_5Na$ 268.1161, found 268.1175 $(M+Na)^+$.

(*E*)-But-2-en-1-yl 2-((*tert*-butoxycarbonyl)amino)acetate (227)



To a solution of *N*-Boc-Gly-OH **184** (1.05 g, 6.0 mmol, 1 equiv.), catalytic DMAP and crotyl alcohol **226** (1.54 mL, 18 mmol, 3 equiv.) in DCM (5 mL) was added a solution of *N*,*N*'-dicyclohexylcarbodiimide (1.40 g, 6.6 mmol, 1.1 equiv.) in DCM (5 mL) and stirred at room temperature for 20 hours. The slurry was diluted with ether (40 mL) and filtered through a pad of celite. The filtrate was washed with aqueous HCl (1 N, 3 × 50 mL), saturated sodium bicarbonate solution (3 × 50 mL) and brine (3 × 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was taken up in ether (50 mL), filtered through a second pad of celite and concentrated *in vacuo* to afford the title compound as a brown oil and was used without any further purification (1.25 g, 92%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.45 (s, 9H, $(CH_3)_3COCON$), 1.73 (d, 3H, *J* = 6.5 Hz,$OCH_2CH=CHCH_3$), 3.92 (d, 2H, *J* = 5.2 Hz, $OCH_2CH=CHCH_3$), 4.58 (d, 2H, *J* = 6.6 Hz, $NHCH_2CO_2$), 4.99 (br, 1H, N*H*), 5.59 (m, 1H, $OCH_2CH=CHCH_3$), 5.80 (m, 1H, $OCH_2CH=CHOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.1, 28.7, 42.8, 66.3, 80.2, 124.9, 132.4, 156.1, 170.6. All analytical data is in accordance with reported literature values.[102]

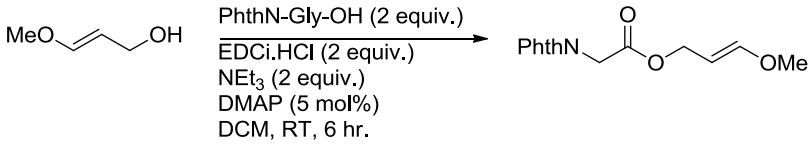
(2*R*,3*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-methylpent-4-enoic acid (179)



Butyllithium (2 mL, 3.3 mmol, 1.6 M solution in hexane) was added to a solution of diisopropylamine (0.56 mL, 4 mmol) in THF (3 mL) at -20 °C. This solution was stirred for 20 minutes, then cooled to -78 °C and a solution of (*E*)-but-2-en-1-yl 2-((*tert*-butoxycarbonyl)amino)acetate **227** (0.22 g, 1.5 mmol) in THF (1.5 mL) was added. After 5 minutes a solution of zinc chloride (1.7 mL, 1 M in ether) was added and then warmed to room temperature. After 4 hours and completion was observed by TLC, a solution of hydrochloric acid (1 N, 3 mL) was added and then concentrated *in vacuo*. The residue was taken up in ether (10 mL), washed with a solution of hydrochloric acid (1 N, 2 × 10 mL). The ether was then extracted with NaOH (1 N, 2 × 10 mL), and the aqueous phases combined, acidified to pH 4 with acetic acid and extracted with ether (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title

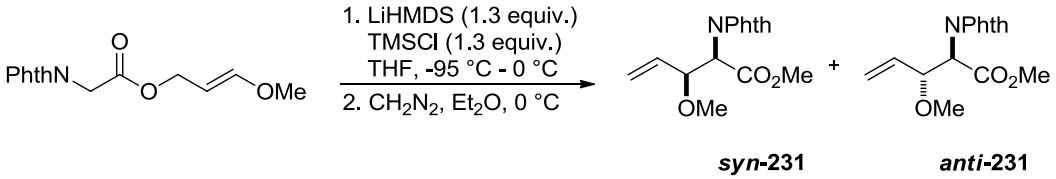
compound as a colourless oil (0.18 g, 84%, dr >25:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.10 (d, 3H, *J* = 6.0 Hz, H_2C=CHCHCH_3), 2.68 – 2.71 (m, 1H, H_2C=CHC*H*CH_3), 4.20 – 4.24 (m, 1H, NC*H*CO_2), 4.96 – 5.1 (m, 2H, *H*$_2$C=CHCHCH$_3$), 5.4 – 5.8 (m, 1H, H_2C=C*H*CHCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.9, 28.1, 40.2, 57.3, 79.7, 115.9, 138.6, 157.0, 175.1. All analytical data is in accordance with reported literature values.[102]

(*E*)-3-Methoxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate (229)



EDCi.HCl (2.18 g, 11.4 mmol), triethylamine (1.57 mL, 11.4 mmol), phthaloyl glycine **228** (2.33 g, 11.4 mmol), catalytic DMAP and (*E*)-3-(methoxy)prop-2-enol **224** (0.50 g, 5.70 mmol) were combined according to general procedure 3, to afford the title compound as a white solid (1.30 g, 84%). MP: 55 - 58 °C; FTIR (film/cm^{-1}) υ_{max}: 2993.7, 2880.3, 1757.6, 1736.1, 1718.0, 1671.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.58 (s, 3H, OC*H*$_3$), 4.43 (s, 2H, NC*H*$_2$CO$_2$), 4.61 (d, 2H, *J* = 8.2 Hz, OC*H*$_2$CH=CHO), 4.92 (dt, 1H, *J* = 12.6, 8.2 Hz, OCH$_2$C*H*=CHO), 6.65 (d, 1H, *J* = 12.6 Hz, OCH$_2$CH=C*H*O), 7.77 – 7.73 (m, 2H, Ar-*H* Phth), 7.91 – 7.88 (m, 2H, Ar-*H*, Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 56.2, 64.2, 96.3, 123.6, 132.1, 134.2, 154.0, 167.3, 167.5; HRMS (ESI, +ve) *m/z*: calcd. for $C_{14}H_{13}NO_5Na$ 298.0692, found 298.0675 $(M+Na)^+$.

(±)-(*2R,3R*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-methoxypent-4-enoate (231)

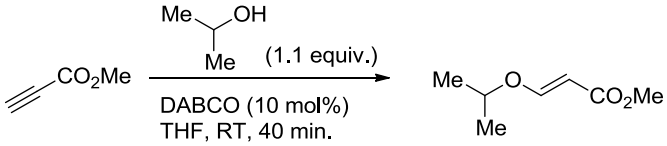


***syn*-231** ***anti*-231**

(*E*)-3-Methoxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate **229** (0.28 g, 1.03 mmol, 1 equiv.), TMSCl (0.15 g, 1.34 mmol, 1.3 equiv.) and LiHMDS (1.24 mL, 1.24 mmol, 1.3 equiv) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (4:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.22 g, 74%, dr 11:1). FTIR (film/cm^{-1}) υ_{max}: 3086.6, 2987.0, 2954.1, 2828.2, 1778.0, 1750.5, 1720.0, 1644.7, 1613.9; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 3.21 (s, 3H, OC*H*$_3$), 3.71 (s, 3H, CO$_2$C*H*$_3$), 4.53 (app. t, 1H, *J* = 8.2 Hz,

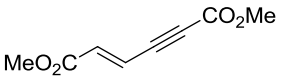
CH_2=CHC*H*O), 4.87 (d, 1H, *J* = 8.2 Hz, NC*H*CO_2), 5.38 (dt, 1H, *J* = 10.1, 1.3 Hz, C*H*$_2$=CHCH), 5.43 (dt, 1H, *J* = 17.1, 1.3 Hz, C*H*$_2$=CHCH), 5.85 (ddd, 1H, *J* = 17.1, 10.1, 8.2 Hz, CH_2=C*H*CH), 7.72 – 7.75 (m, 2H, Ar-*H* Phth), 7.84 – 7.89 (m, 2H, Ar-*H* Phth); *anti* δ: 3.39 (s, 3H, OC*H*$_3$), 3.75 (s, 3H, CO_2C*H*$_3$), 4.67 (t, 1H, *J* = 9.1 Hz, H_2C=CHC*H*O), 5.00 (d, 1H, *J* = 9.1 Hz, NC*H*CO_2), 5.16 (dt, 1H, *J* = 10.7, 1.2 Hz, *H*$_2$C=CHCH), 5.25 (dt, 1H, *J* = 17.7, 1.2 Hz, *H*$_2$C=CHCHO), 5.59 (ddd, 1H, *J* = 17.7, 10.7, 6.8 Hz, H_2C=C*H*CHO), 7.72 – 7.75 (m, 2H, Ar-*H* Phth), 7.84 – 7.89 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 52.5, 55.7, 56.7, 78.2, 119.9, 123.5, 131.8, 134.1, 135.0, 167.5, 167.8; *anti* δ: 52.7, 54.0, 56.9, 80.4, 120.7, 123.6, 132.0, 133.7, 134.3, 167.4, 167.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_{15}H_{15}NO_5Na$ 312.0848, found 312.0831 $(M+Na)^+$.

(*E*)-Methyl 3-isopropoxyacrylate (233)



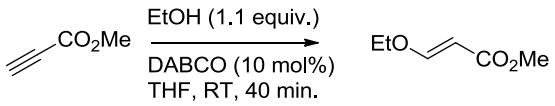
DABCO (0.26 g, 2.38 mmol) in THF (40 mL), 2-propanol (1.43 g, 2.62 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colourless oil (2.4 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.22 (d, 6H, *J* = 6.4 Hz, (C*H*$_3$)$_2$CHO), 3.63 (s, 3H, CO_2C*H*$_3$), 4.17 (sept, 1H, *J* = 6.4 Hz, $(CH_3)_2$C*H*O), 5.17 (d, 1H, *J* = 12.9 Hz, OCH=C*H*CO_2CH_3), 7.47 (d, 1H, *J* = 12.9 Hz, OC*H*=CHCO_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.9, 50.9, 75.6, 96.8, 161.6, 168.4. All analytical data is in accordance with reported literature values.[163]

(*E*)-Dimethyl hex-2-en-4-ynedioate (234)



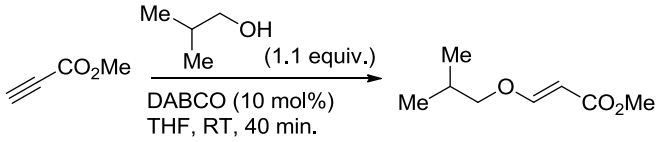
FTIR (film/cm^{-1}) υ_{max}: 3025.4, 3019.7, 2195.0, 1709.1, 1695.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.80 (s, 3H, CO_2C*H*$_3$), 3.83 (s, 3H, CO_2C*H*$_3$), 6.48 (d, 1H, *J* = 16.0 Hz, H_3COCOC*H*=CHC≡C), 6.79 (d, 1H, *J* = 16.0 Hz, H_3COCOCH=C*H*C≡C); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.3, 53.0, 81.8, 86.7, 121.7, 135.0, 153.5, 165.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_8H_8O_4Na$ 191.0320, found 191.0329 $(M+Na)^+$.

(*E*)-Methyl 3-ethoxyacrylate (235)



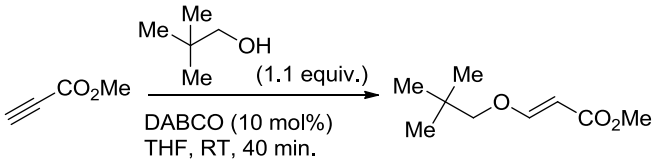
DABCO (0.26 g, 2.38 mmol) in THF (40 mL), ethanol (1.09 g, 26.2 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colourless oil (2.73 g, 88%). FTIR (film/cm^{-1}) υ_{max}: 3095.5, 2986.2, 2952.0, 2903.0, 2846.8, 1712.1, 1626.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.31 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 3.66 (s, 3H, CO$_2$C*H*$_3$), 3.88 (q, 2H, *J* = 7.0 Hz, CH$_3$C*H*$_2$O), 5.17 (d, 1H, *J* = 12.6 Hz, OCH=C*H*CO$_2$CH$_3$), 7.56 (d, 1H, *J* = 12.6 Hz, OC*H*=CHCO$_2$CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.4, 51.0, 66.7, 96.0, 162.4, 168.3; HRMS (ESI, +ve) *m/z*: calcd. for $C_7H_{14}O_3Na$ 153.0528, found 153.0519 $(M+Na)^+$.

(*E*)-Methyl 3-isobutoxyacrylate (236)



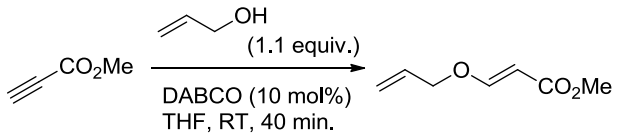
DABCO (0.27 g, 2.38 mmol) in THF (150 mL), 2-methyl-1-propanol (1.93 g, 26.2 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (15:1 Pet/EtOAc) to afford the title compound as a colourless oil (3.37 g, 86%). FTIR (film/cm^{-1}) υ_{max}: 2961.6, 2877.0, 1712.3, 1628.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.91 (d, 6H, *J* = 6.7 Hz, (C*H*$_3$)$_2$CHCH$_2$O), 1.95 (oct, 1H, *J* = 6.7 Hz, (CH$_3$)$_2$C*H*CH$_2$O), 3.56 (d, 2H, *J* = 6.7 Hz, (CH$_3$)$_2$CHC*H*$_2$O), 3.64 (s, 3H, CO$_2$C*H*$_3$), 5.14 (d, 1H, *J* = 12.7 Hz, OCH=C*H*CO$_2$CH$_3$), 7.55 (d, 1H, *J* = 12.7 Hz, OC*H*=CHCO$_2$CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.8, 28.0, 50. 9, 77.4, 95.8, 162.8, 168.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_8H_{14}O_3Na$ 159.1021, found 159.1023 $(M+Na)^+$.

(*E*)-Methyl 3-(neopentyloxy)acrylate (237)



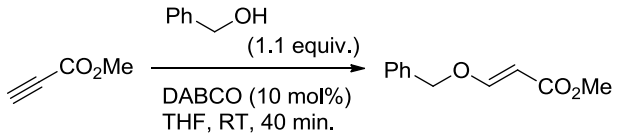
DABCO (0.27 g, 2.38 mmol) in THF (150 mL), neopentyl alcohol (2.31 g, 26.2 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colourless oil (3.98 g, 92%). FTIR (film/cm^{-1}) υ_{max}: 2958.5, 2871.7, 1715.5, 1645.5, 1627.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (s, 9H, $(CH_3)_3CCH_2O$), 3.50 (s, 2H, $(CH_3)_3CCH_2O$), 3.71 (s, 3H, CO_2CH_3), 5.20 (d, 1H, J = 12.6 Hz, $OCH{=}CHCO_2CH_3$), 7.63 (d, 1H, J = 12.6 Hz, $OCH{=}CHCO_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.3, 31.8, 51.0, 81.1, 95.7, 163.3, 168.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_9H_{16}O_3Na$ 195.0997, found 195.0985 $(M+Na)^+$.

(*E*)-Methyl 3-(allyloxy)acrylate (238)



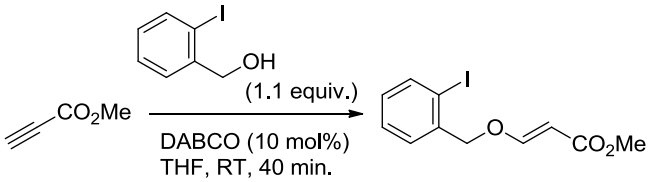
DABCO (0.26 g, 2.38 mmol) in THF (200 mL), allyl alcohol (1.37 g, 26.2 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colorless oil (2.85 g, 85%). FTIR (film/cm^{-1}) υ_{max}: 3092.8, 2922.1, 2952.2, 2876.0, 2846.9, 1713.9, 1625.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.60 (s, 3H, CO_2CH_3), 4.30 (dt, 2H, J = 5.3, 1.6 Hz, $CH_2{=}CHCH_2O$), 5.16 (d, 1H, J = 12.6 Hz, $OCH{=}CHCO_2CH_3$), 5.22 (dq, 1H, J = 10.3, 1.6 Hz, $CH_2{=}CHCH_2O$), 5.28 (dq, 1H, J = 17.2, 1.6 Hz, $CH_2{=}CHCH_2O$), 5.85 (ddt, 1H, J = 17.2, 10.3, 5.3 Hz, $CH_2{=}CHCH_2O$), 7.49 (d, 1H, J = 12.6 Hz, $OCH{=}CHCO_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 50.9, 71.5, 96.8, 118.7, 131.7, 161.9, 167.9; HRMS (ESI, +ve) *m/z*: calcd. for $C_7H_{10}O_3Na$ 165.0528, found 165.0520 $(M+Na)^+$.

(*E*)-Methyl 3-(benzyloxy)acrylate (239)



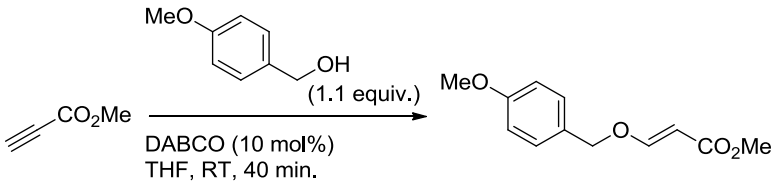
DABCO (0.11 g, 1.00 mmol) in THF (40 mL), benzyl alcohol (1.08 g, 11.0 mmol) and methyl propiolate **232** (0.84 g, 10.0 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colourless oil (1.65 g, 86%). FTIR (film/cm^{-1}) υ_{max}: 3092.1, 3065.9, 3034.0, 2950.5, 2882.2, 2844.8, 1712.2, 1644.4, 1625.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.71 (s, 3H, CO_2CH_3), 4.91 (s, 2H, $PhCH_2O$), 5.34 (d, 1H, *J* = 12.7 Hz, $OCH=CHCO_2CH_3$), 7.42 – 7.34 (m, 5H, Ar-*H* Ph), 7.69 (d, 1H, *J* = 12.7 Hz, $OCH=CHCO_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.1, 72.9, 97.2, 127.7, 128.5, 128.7, 135.2, 162.1, 168.0; HRMS (ESI, +ve) *m/z*: calcd. for $C_{11}H_{12}O_3Na$ 215.0684, found 215.0676 $(M+Na)^+$. All data is in accordance with reported literature values.[164]

(*E*)-Methyl 3-(2-iodobenzyloxy)acrylate (240)



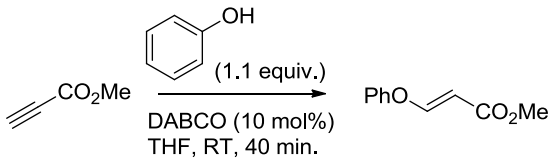
DABCO (0.27 g, 2.38 mmol) in THF (40 mL), 2-iodobenzyl alcohol (6.12 g, 26.2 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (6:1 Pet/EtOAc) to afford the title compound as a white solid (6.85 g, 91%). MP: 40 – 42 °C; FTIR (film/cm^{-1}) υ_{max}: 3091.4, 3052.3, 2947.4, 2909.9, 2855.8, 1713.2, 1640.0, 1623.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.73 (s, 3H, CO_2CH_3), 4.91 (s, 2H, $ArCH_2O$), 5.37 (d, 1H, *J* = 12.5 Hz, $OCH=CHCO_2CH_3$), 7.07 – 7.04 (m, 1H, Ar-*H* Ph), 7.40 – 7.36 (m, 2H, Ar-*H* Ph), 7.71 (d, 1H, *J* = 12.5 Hz, $OCH=CHCO_2CH_3$)), 7.87 (d, 1H, *J* = 8.1 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.2, 76.4, 97.4, 97.5, 128.5, 128.8, 130.1, 137.5, 139.5, 161.7, 167.9; HRMS (ESI, +ve) *m/z*: calcd. for $C_{11}H_{12}IO_3$ 318.9831, found 318.9842 $(M+H)^+$.

(*E*)-Methyl 3-(4-methoxybenzyloxy)acrylate (241)



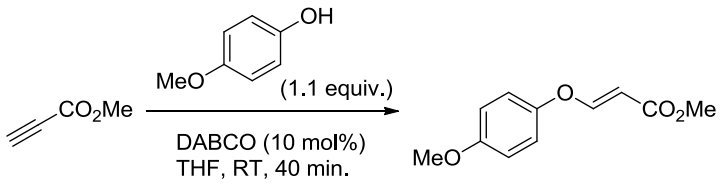
DABCO (0.11 g, 1.00 mmol) in THF (40 mL), 4-methoxybenzyl alcohol (1.38 g, 11.0 mmol) and methyl propiolate **232** (0.84 g, 10.0 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colourless oil (1.73 g, 78%). FTIR (film/cm^{-1}) υ_{max}: 3092.5, 3000.2, 2951.2, 2910.2, 2838.7, 1711.3, 1624.5, 1586.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.71 (s, 3H, CO_2CH_3), 3.83 (s, 3H, CH_3OAr), 4.84 (s, 2H, $ArCH_2O$), 5.32 (d, 1H, *J* = 12.5 Hz, $OCH=CHCO_2CH_3$), 6.92 (m, 2H, Ar-*H* Ph), 7.28 (m, 2H, Ar-*H* Ph), 7.67 (d, 1H, *J* = 12.5 Hz, $OCH=CHCO_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.1, 55.3, 72.8, 97.0, 114.1, 127.2, 129.6, 159.9, 162.2, 168.1; HRMS (ESI, +ve) *m/z:* calcd. for $C_{12}H_{14}O_4Na$ 245.7900, found 245.0783 $(M+Na)^+$.

(*E*)-Methyl 3-phenoxyacrylate (242)



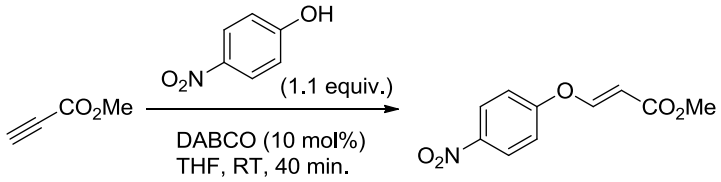
DABCO (0.27 g, 2.38 mmol) in THF (100 mL), phenol (2.46 g, 26.2 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colourless oil (4.35 g, 98%). FTIR (film/cm^{-1}) υ_{max}: 3078.8, 3044.2, 2994.4, 2952.0, 2906.4, 2845.6, 1715.4, 1649.1, 1589.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.74 (s, 3H, CO_2CH_3), 5.58 (d, 1H, *J* = 12.4 Hz, $PhOCH=CHCO_2CH_3$), 7.08 (d, 2H, *J* = 8.0 Hz, Ar-*H* Ph), 7.21 (t, 1H, *J* = 8.0 Hz, Ar-*H* Ph), 7.39 (t, 2H, *J* = 8.0 Hz, Ar-*H* Ph), 7.83 (d, 1H, *J* = 12.4 Hz, $PhOCH=CHCO_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.3, 101.8, 118.0, 125.0, 130.0, 155.9, 159.2, 167.6; HRMS (ESI, +ve) *m/z: calcd*. for $C_{10}H_{11}O_3$ 179.0708, found 179.0701 $(M+H)^+$.

(*E*)-Methyl 3-(4-methoxyphenoxy)acrylate (243)



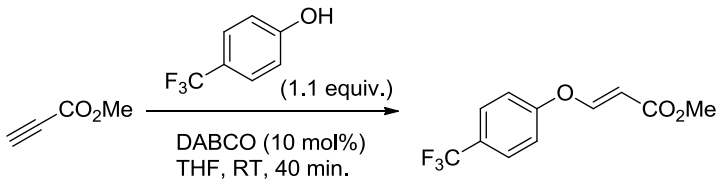
DABCO (0.27 g, 2.38 mmol) in THF (150 mL), 4-methoxyphenol (3.24 g, 26.2 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (6:1 Pet/EtOAc) to afford the title compound as a colourless oil (4.30 g, 82%). FTIR (film/cm^{-1}) υ_{max}: 3078.4, 2994.2, 2948.4, 2843.3, 1715.3, 1649.8, 1629.6, 1573.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.73 (s, 3H, CO_2CH_3), 3.81 (s, 3H, CH_3OAr), 5.48 (d, 1H, *J* = 12.6 Hz, OCH=C*H*CO_2CH_3), 6.89 (m, 2H, Ar-*H* Ph), 7.00 (m, 2H, Ar-*H* Ph), 7.76 (d, 1H, *J* = 12.6 Hz, OC*H*=CHCO_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.7, 56.1, 101.3, 115.3, 119.8, 149.9, 157.3, 160.8, 168.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{11}H_{12}O_4Na$ 231.0633, found 231.0619 $(M+Na)^+$.

(*E*)-Methyl 3-(4-nitrophenyloxy)acrylate (244)



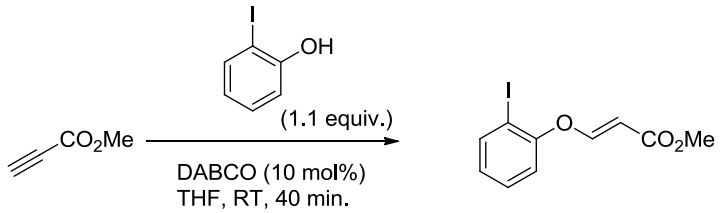
DABCO (0.28 g, 2.51 mmol) in THF (40 mL), 4-nitrophenol (3.85 g, 27.6 mmol) and methyl propiolate **232** (2.11 g, 25.1 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (6:1 Pet/EtOAc) to afford the title compound as a yellow solid (5.72 g, 98%). MP: 133 – 136 °C; FTIR (film/cm^{-1}) υ_{max}: 3505.5, 2987.7, 1717.0, 1653.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.78 (s, 3H, CO_2CH_3), 5.79 (d, 1H, *J* = 12.5, OCH=C*H*CO_2CH_3)), 7.18 – 7.24 (m, 2H, Ar-*H* Ph), 7.82 (d, 1H, *J* = 12.5, OC*H*=CHCO_2CH_3), 8.28 - 8.31(m, 2H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.64, 105.08, 117.60, 126.09, 144.38, 155.92, 160.18, 166.76; HRMS (ESI, +ve) *m/z*: calcd. for $C_{10}H_9NO_5Na$ 246.0378, found 246.0380 $(M+Na)^+$.

(*E*)-Methyl 3-(4-trifluoromethylphenyloxy)acrylate (245)



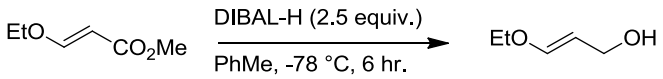
DABCO (0.05 g, 0.45 mmol) in THF (150 mL), 4-trifluoromethylphenol (0.80 g, 4.97 mmol) and methyl propiolate **232** (0.38 g, 4.52 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (15:1 Pet/EtOAc) to afford the title compound as a white solid (1.10 g, 93%). MP: 60 – 61 °C; FTIR (film/cm^{-1}) υ_{max}: 3121.9, 3080.6, 3037.8, 3004.5, 2959.9, 1713.7, 1663.7, 1614.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.74 (s, 3H, CO_2CH_3), 5.66 (d, 1H, *J* = 12.2 Hz, OCH=C*H*CO_2CH_3), 7.16 (m, 2H, Ar-*H* Ph), 7.64 (m, 2H, Ar-*H* Ph), 7.80 (d, 1H, *J* = 12.2 Hz, OC*H*=CHCO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.4, 103.6, 117.8, 122.7, 124.9, 126.7, 128.4 (q, *J* = 4.0 Hz), 157.2, 158.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{11}H_9F_3O_3Na$ 177.0528, found 177.0522 $(M+Na)^+$.

(*E*)-Methyl 3-(2-iodophenyloxy)acrylate (246)



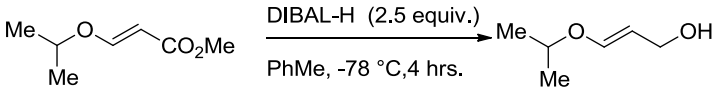
DABCO (0.09 g, 0.83 mmol) in THF (150 mL), 2-iodophenol (2.00 g, 9.16 mmol) and methyl propiolate **232** (0.70 g, 8.33 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (6:1 Pet/EtOAc) to afford the title compound as a colourless oil (2.52 g, 93%). FTIR (film/cm^{-1}) υ_{max}: 3081.0, 2995.6, 2949.8, 1715.4, 1650.5, 1630.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.74 (s, 3H, CO_2CH_3), 5.52 (d, 1H, *J* = 12.4 Hz, OCH=C*H*CO_2CH_3), 6.96 (t, 1H, *J* = 7.8 Hz, Ar-*H* Ph), 7.07 (d, 1H, *J* = 7.8 Hz, Ar-*H* Ph), 7.38 (t, 1H, *J* = 7.8 Hz, Ar-*H* Ph), 7.72 (d, 1H, *J* = 12.4 Hz, OC*H*=CHCO_2CH_3), 7.85 (d, 1H, *J* = 7.8 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.4, 87.8, 102.3, 119.1, 127.0, 130.0, 140.0, 155.1, 159.0, 167.3; HRMS (ESI, +ve) *m/z*: calcd. for $C_{10}H_{10}IO_3$ 304.9675, found 304.9657 $(M+H)^+$.

(*E*)-3-(Ethoxy)prop-2-enol (247)



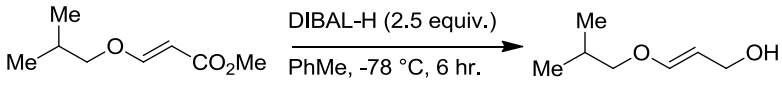
(*E*)-Methyl 3-ethoxyacrylate **235** (1.59 g, 12.2 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (0.90 g, 75%). FTIR (film/cm^{-1}) υ_{max}: 3355.9, 2980.9, 2877.4, 1672.3, 1654.1; ^{1}H NMR (500 MHz, d_6-DMSO) δ: 1.19 (t, 3H, *J* = 7.1 Hz, C*H*$_3$CH$_2$O), 3.70 (q, 2H, *J* = 7.1 Hz, CH$_3$C*H*$_2$O), 3.83 (ddd, 2H, *J* = 6.9, 5.6, 1.3 Hz, OCH=CHC*H*$_2$OH), 4.40 (t, 1H, *J* = 5.6 Hz, O*H*), 4.86 (dt, 1H, *J* = 12.9, 6.9 Hz, OCH=C*H*CH$_2$OH), 6.42 (d, 1H, *J* = 12.9 Hz, OC*H*=CHCH$_2$OH); ^{13}C NMR (125 MHz, d_6-DMSO) δ: 15.1, 59.0, 64.6, 104.4, 148.5.

(*E*)-3-(Isopropyloxy)prop-2-enol (248)



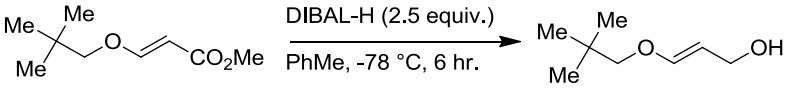
(*E*)-Methyl 3-(isopropoxy)acrylate **233** (2.00 g, 13.8 mmol) was reduced according to general procedure 5 to afford the title compound as a yellow oil (1.19 g, 74%). FTIR (film/cm^{-1}) υ_{max}: 3371.8, 2976.5, 2931.2, 2874.6, 1670.6, 1650.9. ^{1}H NMR (500 MHz, d_6-acetone) δ: 1.15 (d, 6H, *J* = 6.2 Hz, (C*H*$_3$)$_2$CHO), 3.81 (app. t, 2H, *J* = 6.5 Hz, OCH=CHC*H*$_2$OH), 4.00 (quin, 1H, *J* = 6.2 Hz, (CH$_3$)$_2$C*H*O), 4.36 (t, 1H, *J* = 6.5 Hz, OCH=CHCH$_2$O*H*), 4.88 (dt, 1H, *J* = 12.5, 6.5 Hz, OCH=C*H*CH$_2$OH), 6.33 (d, 1H, *J* = 12.5 Hz, OC*H*=CHCH$_2$OH). ^{13}C NMR (125 MHz, d_6-acetone) δ: 22.4, 59.0, 72.3, 105.7, 147.6.

(*E*)-3-(Isobutyloxy)prop-2-enol (249)



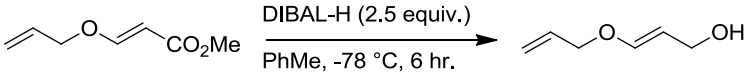
(*E*)-Methyl 3-(isobutyloxy)acrylate **236** (1.38 g, 8.72 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (0.57 g, 85%). FTIR (film/cm^{-1}) υ_{max}: 3346.3, 2958.9, 2932.0, 2873.9, 1671.6, 1653.0; ^{1}H NMR (300 MHz, d_6-acetone) δ: 0.79 (d, 6H, *J* = 6.7 Hz, (C*H*$_3$)$_2$CHCH$_2$O), 1.77 (oct, 1H, *J* = 6.7 Hz, (CH$_3$)$_2$C*H*CH$_2$O), 3.15 (t, 1H, *J* = 5.5 Hz, O*H*) 3.32 (d, 2H, *J* = 6.7 Hz, (CH$_3$)$_2$CHC*H*$_2$O), 3.81 (ddd, 2H, *J* = 7.0, 5.5, 1.1 Hz, OCH=CHC*H*$_2$OH), 4.82 (dt, 1H, *J* = 12.6, 7.0 Hz, OCH=C*H*CH$_2$OH), 6.35 (d, 1H, *J* = 12.6 Hz, OC*H*=CHCH$_2$OH); ^{13}C NMR (125 MHz, d_6-acetone) δ: 19.7, 29.3, 60.7, 76.5, 104.9, 150.3.

(*E*)-3-(Neopentyloxy)prop-2-en-1-ol (250)



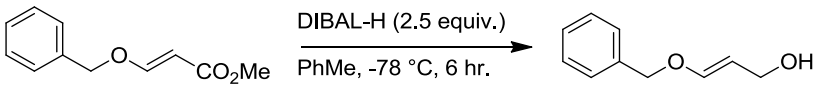
(*E*)-Methyl 3-(neopentyloxy)acrylate **237** (1.36 g, 7.90 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (0.92 g, 86%). FTIR (film/cm^{-1}) υ_{max}: 3343.4, 3063.7, 2957.6, 2904.4, 2869.8, 1670.6, 1653.0; ^{1}H NMR (500 MHz, d_6-acetone) δ: 0.94 (s, 9H, (C*H*$_3$)$_3$CCH$_2$O), 3.30 (t, 1H, *J* = 7.1 Hz, O*H*), 3.36 (s, 2H, (CH$_3$)$_3$CC*H*$_2$O), 3.95 (app. t, 2H, *J* = 7.1 Hz, OCH=CHC*H*$_2$OH), 4.96 (dt, 1H, *J* = 12.7, 7.1 Hz, OCH=C*H*CH$_2$OH), 6.52 (d, 1H, *J* = 12.7 Hz, OC*H*=CHCH$_2$OH); ^{13}C NMR (125 MHz, d_6-acetone) δ: 25.8, 31.3, 59.4, 78.7, 103.3, 149.4.

(*E*)-3-(Allyloxy)prop-2-enol (251)



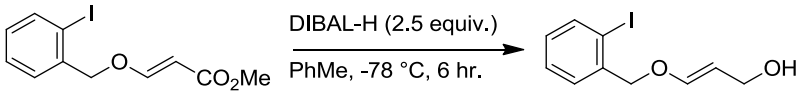
(*E*)-Methyl 3-(allyloxy)acrylate **238** (1.38 g, 9.71 mmol) was reduced according to general procedure 5 to afford the title compound as a yellow oil (0.78 g, 71%). FTIR (film/cm^{-1}) υ_{max}: 3350.6, 2923.2, 2869.7, 1671.8, 1654.4; ^{1}H NMR (500 MHz, d_6-DMSO) δ: 3.83 (ddd, 2H, *J* = 7.0, 5.5, 1.2 Hz, CH$_2$=CHC*H*$_2$O), 4.21 (dt, 2H, *J* = 5.2, 1.7 Hz, OCH=CHC*H*$_2$OH), 4.43 (t, 1H, *J* = 5.5 Hz, CH$_2$O*H*), 4.92 (dt, 1H, *J* = 13.8, 6.9 Hz, OCH=C*H*CH$_2$OH), 5.20 (dq, 1H, *J* = 10.4, 1.8 Hz, C*H*$_2$=CHCH$_2$O), 5.31 (dq, 1H, *J* = 17.3, 1.8 Hz, C*H*$_2$=CHCH$_2$O), 5.94 (ddt, 1H, *J* = 17.3, 10.4, 5.4 Hz, CH$_2$=C*H*CH$_2$O), 6.44 (d, 1H, *J* = 13.8 Hz, OC*H*=CHCH$_2$OH); ^{13}C NMR (125 MHz, d_6-DMSO) δ: 58.5, 69.9, 105.1, 117.6, 134.3, 148.2.

(*E*)-3-(Benzyloxy)prop-2-enol (252)



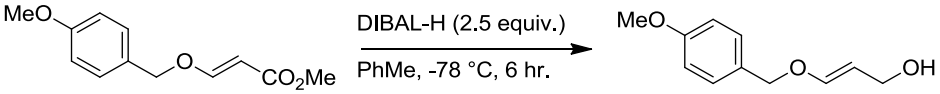
(*E*)-Methyl 3-(benzyloxy)acrylate **239** (2.15 g, 11.2 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (1.56 g, 80%). FTIR (film/cm^{-1}) υ_{max}: 3348.7, 3064.7, 3033.4, 2926.1, 2871.1, 1670.6, 1652.6; ^{1}H NMR (500 MHz, d_6-DMSO) δ: 3.86 (t, 2H, *J* = 5.3 Hz, OCH=CHC*H*$_2$OH), 4.47 (t, 1H, *J* = 5.3 Hz, CH$_2$O*H*), 4.75 (s, 2H, PhC*H*$_2$O), 5.02 (m, 1H, OCH=C*H*CH$_2$OH), 6.55 (d, 1H, *J* = 13.1 Hz, OC*H*=CHCH$_2$OH), 7.32 – 7.39 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, d_6-DMSO) δ: 58.9, 71.0, 105.4, 126.9, 127.1, 128.2, 128.5, 128.8, 137.7, 148.4.

(*E*)-3-(2-Iodobenzyloxy)prop-2-enol (253)



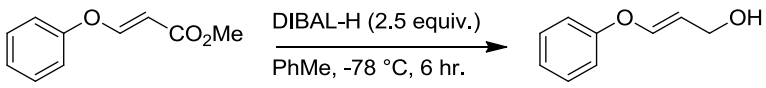
(*E*)-Methyl 3-(2-iodobenzyloxy)acrylate **240** (1.08 g, 3.40 mmol) was reduced according to general procedure 5 to afford the product as a colourless oil (0.88 g, 89%). FTIR (film/cm^{-1}) υ_{max}: 3391.9, 3062.1, 2924.5, 2873.2, 1774.8, 1746.7, 1718.4, 1670.1, 1652.1; ^{1}H NMR (500 MHz, d_6-acetone) δ: 3.44 (t, 1H, *J* = 7.0 Hz, CH_2OH), 4.01 (t, 1H, *J* = 7.0 Hz, OCH=CHCH_2OH), 4.78 (s, 2H, ArCH_2O), 5.14 (dt, 1H, *J* = 12.3, 7.0 Hz, OCH=C*H*CH_2OH), 6.63 (d, 1H, *J* = 12.3 Hz, OC*H*=CHCH_2OH), 7.11 (td, 1H, *J* = 7.6, 1.7 Hz, Ar-*H* Ph), 7.43 – 7.50 (m, 2H, Ar-*H* Ph), 7.91 (dd, 1H, *J* = 7.6, 1.0 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, d_6-acetone) δ: 59.2, 74.6, 97.2, 105.2, 128.4, 129.0, 129.7, 139.3, 139.5, 148.1.

(*E*)-3-(4-Methoxybenzyloxy)prop-2-enol (254)



(*E*)-Methyl 3-(4-methoxybenzyloxy)acrylate **241** (1.02 g, 4.59 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (0.78 g, 72%). FTIR (film/cm^{-1}) υ_{max}: 3303.5, 2922.6, 2872.5, 1650.2, 1613.5, 1586.9; ^{1}H NMR (500 MHz, d_6-DMSO) δ: 3.75 (s, 3H, CH_3OAr), 3.84 (t, 2H, *J* = 7.1 Hz, OCH=CHCH_2OH), 4.45 (t, 1H, *J* = 7.1 Hz, CH_2OH), 4.66 (s, 2H, ArCH_2O), 4.98 (dt, 1H, *J* = 12.8, 7.1 Hz, OCH=C*H*CH_2OH), 6.52 (d, 1H, *J* = 12.8 Hz, OC*H*=CHCH_2OH), 6.93 – 7.01 (m, 2H, Ar-*H* Ph), 7.29 – 7.35 (m, 2H, Ar-*H* Ph); ^{13}C NMR (125 MHz, d_6-DMSO) δ: 55.5, 58.9, 70.8, 105.2, 113.9, 128.4, 129.6, 148.4, 159.4.

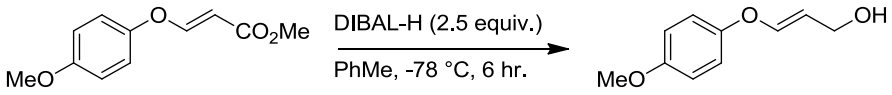
(*E*)-3-(Phenyloxy)prop-2-en-1-ol (255)



(*E*)-Methyl 3-(phenyloxy)acrylate **242** (1.02 g, 5.72 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (0.60 g, 53%). FTIR (film/cm^{-1}) υ_{max}: 3343.9, 3030.2, 2924.9, 2864.2, 1673.5, 1592.3; ^{1}H NMR (500 MHz, d_6-acetone) δ: 3.70 (t, 1H, *J* = 6.6 Hz, CH_2OH), 4.11 (app. t, 2H, *J* = 6.6 Hz, OCH=CHCH_2OH), 5.49 (dt, 1H, *J* = 12.3, 6.6 Hz, OCH=C*H*CH_2OH), 6.81 (d, 1H, *J* = 12.3 Hz, OC*H*=CHCH_2OH), 7.04 (d, 2H, *J* = 7.5 Hz, Ar-*H* Ph), 7.08 (t, 1H, *J* = 7.5 Hz,

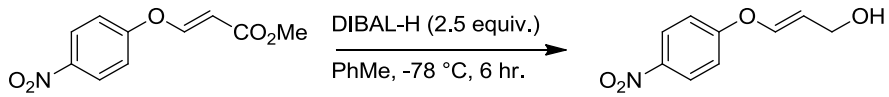
Ar-*H* Ph), 7.36 (d, 2H, *J* = 7.5 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, d_6-acetone) δ: 58.4, 112.5, 116.4, 122.8, 129.7, 143.8, 157.2.

(*E*)-3-(4-Methoxyphenyloxy)prop-2-en-1-ol (256)



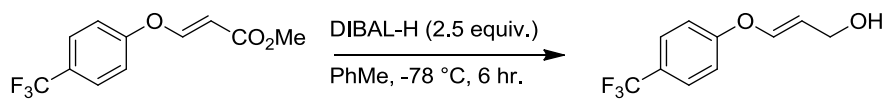
(*E*)-Methyl 3-(4-methoxyphenyloxy)acrylate **243** (1.15 g, 5.52 mmol) was reduced according to general procedure 5, to afford the title compound as a colourless oil (0.64 g, 64%). FTIR (film/cm^{-1}) υ_{max}: 3348.5, 3048.5, 3002.8, 2950.5, 2836.4, 1672.4, 1609.4, 1592.4; ^{1}H NMR (500 MHz, d_6-acetone) δ: 4.10 (t, 1H, *J* = 5.6 Hz, CH_2OH), 4.28 (s, 3H, CH_3OAr), 4.58 (t, 2H, *J* = 5.6 Hz, OCH=CHCH_2OH), 5.88 (dt, 1H, *J* = 12.2, 5.6 Hz, OCH=C*H*CH$_2$OH), 7.22 (d, 1H, *J* = 12.2 Hz, OC*H*=CHCH$_2$OH), 7.40 – 7.44 (m, 2H, Ar-*H* Ph), 7.46 – 7.49 (m, 2H, Ar-*H* Ph); ^{13}C NMR (125 MHz, d_6-acetone) δ: 55.0, 58.5, 111.0, 114.7, 117.9, 145.3, 150.9, 155.7.

(*E*)-3-(4-Nitrophenoxy)prop-2-en-1-ol (257)



(*E*)-Methyl 3-(4-nitrophenyloxy)acrylate **244** (2.23 g, 10 mmol) was reduced according to general procedure 5 to afford the title compound as a yellow solid (1.93 g, 89%). FTIR (film/cm^{-1}) υ_{max}: 3012.7, 3017.3, 2977.1, 1674.9, 1614.8; ^{1}H NMR (500 MHz, d_6-DMSO) δ: 4.18 (dd, 2H, *J* = 6.5, 1.5 Hz, OCH=CHCH_2OH), 5.72 (dt, 1H, *J* = 12.1, 6.5 Hz, OCH=C*H*CH$_2$OH), 6.97 (d, 1H, *J* = 12.1 Hz, OC*H*=CHCH$_2$OH), 7.25 – 7.29 (m, 2H, Ar-*H* Ph), 8.25 – 8.29 (m, 2H, Ar-*H* Ph); ^{13}C NMR (125 MHz, d_6-DMSO) δ: 58.1, 116.1, 116.2, 125.8, 140.2, 141.7, 162.0.

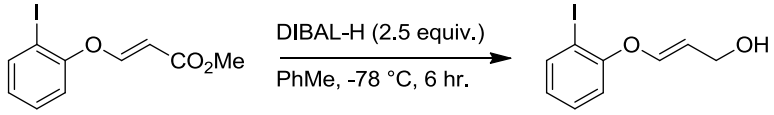
(*E*)-3-(4-Trifluoromethylphenyloxy)prop-2-en-1-ol (258)



(*E*)-Methyl 3-(4-trifluoromethylphenyloxy)acrylate **245** (0.63 g, 2.56 mmol) was reduced according to general procedure 5 to afford the title compound as a yellow oil (0.54 g, 85%). FTIR (film/cm^{-1}) υ_{max}: 3336.9, 2930.5, 2878.6, 1676.3, 1615.1, 1516.1; ^{1}H NMR (500 MHz, d_6-acetone) δ: 3.76 (br, 1H, CH_2OH), 3.96 (dd, 2H, *J* = 6.5, 1.3 Hz, OCH=CHCH_2OH), 5.43 (dt, 1H, *J* = 12.0, 6.5 Hz, OCH=C*H*CH$_2$OH), 6.66 (dt, *J* =

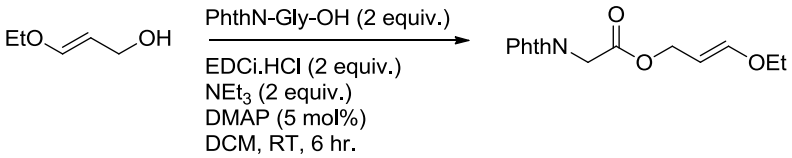
12.0, 1.3 Hz, OC*H*=CHCH$_2$OH), 6.95 – 7.01 (m, 2H, Ar-*H* Ph), 7.42 – 7.46 (m, 2H, Ar-*H*, Ph); ^{13}C NMR (125 MHz, d$_6$-acetone) δ: 59.6, 116.0, 117.7, 125.3, 127.6, 128.4 (q, *J* = 4.0 Hz), 143.8, 161.1.

(*E*)-3-(2-Iodophenyloxy)prop-2-en-1-ol (259)



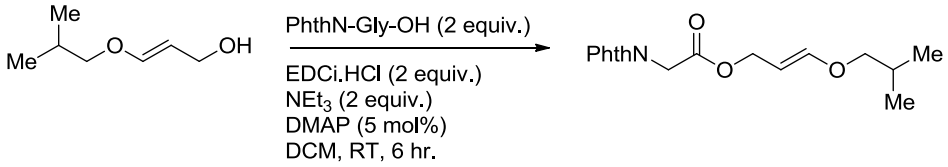
(*E*)-Methyl 3-(2-iodophenyloxy)acrylate **246** (1.34 g, 4.41 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (1.00 g, 82%). FTIR (film/cm^{-1}) υ$_{max}$: 3429.2, 2950.0, 2837.1, 1649.1, 1504.3; ^{1}H NMR (500 MHz, d$_6$-acetone) δ: 3.59 (t, 1H, *J* = 5.7 Hz, CH$_2$O*H*), 3.99 (dt, 2H, *J* = 6.6, 1.4 Hz, OCH=CHC*H*$_2$OH), 5.40 (dt, 1H, *J* = 12.1, 6.6 Hz, OCH=C*H*CH$_2$OH), 6.63 (dt, 1H, *J* = 12.1, 1.4 Hz, OC*H*=CHCH$_2$OH), 6.77 (dt, 1H, *J* = 7.5, 1.4 Hz, Ar-*H* Ph), 6.97 (dd, 1H, *J* = 7.5, 1.4 Hz, Ar-*H* Ph), 7.25 – 7.31 (m, 1H, Ar-*H* Ph), 7.72 (dd, 1H, *J* = 7.9, 1.4 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, d$_6$-acetone) δ: 59.6, 87.4, 115.0, 117.7, 126.2, 131.2, 141.0, 144.9, 157.6.

(*E*)-3-Ethoxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate (261)



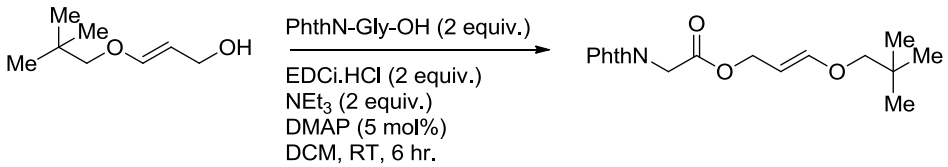
EDCi.HCl (1.58 g, 5.02 mmol), triethylamine (1.15 mL, 5.02 mmol), phthaloyl glycine **228** (1.70 g, 5.02 mmol), catalytic DMAP and (*E*)-3-(ethoxy)prop-2-enol **247** (0.54 g, 2.51 mmol) were combined according to general procedure 3, to afford the title compound as a yellow solid (0.93 g, 78%). MP: 58 – 60 °C; FTIR (film/cm^{-1}) υ$_{max}$: 2983.7, 2939.4, 2890.3, 1777.8, 1745.3, 1717.9, 1671.7, 1671.7, 1653.8; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.29 (t, 3H, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 3.79 (q, 2H, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 4.43 (s, 2H, NC*H*$_2$CO$_2$), 4.60 (d, 2H, *J* = 7.5 Hz, OC*H*$_2$CH=CHO), 4.93 (dt, 1H, *J* = 12.9, 7.5 Hz, OCH$_2$C*H*=CHO), 6.59 (d, 1H, *J* = 12.9 Hz, OCH$_2$CH=C*H*O), 7.76 – 7.74 (m, 2H, Ar-*H* Phth), 7.90 – 7.88 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 14.5, 39.0, 64.4, 65.1, 96.9, 123.6, 123.6, 132.0, 134.2, 153.1, 167.3, 167.5; HRMS (ESI, +ve) *m/z*: calcd. for C$_{15}$H$_{15}$NO$_5$Na 312.0848, found 312.0837 (M+Na)$^+$.

(*E*)-3-Isobutoxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate (262)



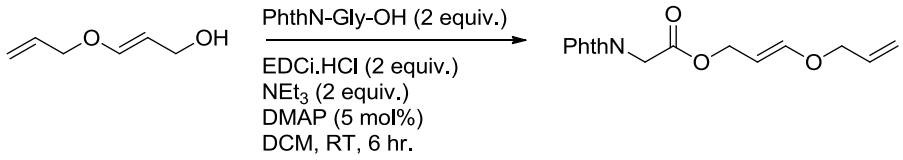
EDCi.HCl (1.69 g, 8.82 mmol), triethylamine (1.22 mL, 8.82 mmol), phthaloyl glycine **228** (1.88 g, 8.82 mmol), catalytic DAMP and (*E*)-3-(isobutyloxy)prop-2-enol **249** (0.57 g, 4.41 mmol) were combined according to general procedure 3 to afford the title compound as a yellow solid (0.85 g, 61%). MP: 65 – 66 °C; FTIR (film/cm^{-1}) υ_{max}: 3066.7, 2959.9, 2874.6, 1777.4, 1723.5, 1670.9, 1652.7, 1616.1; ^{1}HNMR (500 MHz, $CDCl_3$) δ: 0.94 (d, 6H, *J* = 6.9 Hz, $OCH_2CH(CH_3)_2$), 1.94 (oct, 1H, *J* = 6.9 Hz, $OCH_2CH(CH_3)$), 3.47 (d, 2H, *J* = 6.9 Hz, $OCH_2CH(CH_3)$), 4.42 (s, 2H NCH_2CO_2), 4.59 (d, 2H, *J* = 8.2 Hz, OCH_2CH=CHO), 4.91 (dt, 1H, *J* = 12.9, 8.2 Hz, OCH_2CH=CHO), 6.60 (d, 1H, *J* = 12.9 Hz, OCH_2CH=CHO), 7.73 – 7.75 (m, 2H, Ar-*H* Phth), 7.87 – 7.89 (m, 2H, Ar-*H* Phth); ^{13}C NMR(125 MHz, $CDCl_3$) δ: 19.1, 28.1, 39.0, 64.5, 75.9, 96.6, 123.6, 132.0, 134.2, 153.0,167.3, 167.5; HRMS (ESI, +ve) *m/z* calcd. for $C_{17}H_{19}NO_5Na$ 340.1160, found 340.1153 $(M+Na)^+$.

(*E*)-3-(Neopentyl)oxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate (263)



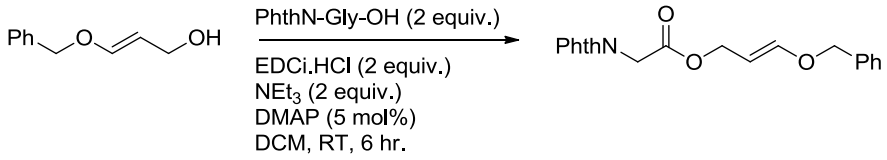
EDCi.HCl (2.68 g, 14.0 mmol), triethylamine (2.00 mL, 14.0 mmol), phthaloyl glycine **228** (2.86 g, 14.0 mmol), catalytic DMAP and (*E*)-3-(neopentyloxy)prop-2-enol **250**(1.00 g) were combined according to general procedure 3 to afford the title compound as a white solid (1.75 g, 76%). MP: 70 – 73 °C; FTIR (film/cm^{-1}) υ_{max}: 3062.5, 2958.1, 2870.0, 1777.7, 1723.9, 1670.8, 1651.4, 1616.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (s, 9H, $OCH_2C(CH_3)_3$), 3.30 (s, 2H, $OCH_2C(CH_3)_3$), 4.36 (s, 2H, NCH_2CO_2), 4.53 (d, 2H, *J* = 8.4 Hz, OCH_2CH=CHO), 4.85 (dt, 1H, *J* = 12.7, 8.4 Hz, OCH_2CH=CHO), 6.58 (d, 1H, *J* = 12.7 Hz, OCH_2CH=CHO), 7.65 – 7.69 (m, 2H, Ar-*H* Phth), 7.78 – 7.81 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.4, 31.6, 39.0, 64.4, 79.8, 96.3, 123.5, 132.0, 134.2, 153.8, 167.2, 167.3; HRMS (ESI, +ve) *m/z* calcd. for $C_{18}H_{21}NO_5Na$ 354.1317, found 354.1322 $(M+Na)^+$.

(*E*)-3-(Allyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate (264)



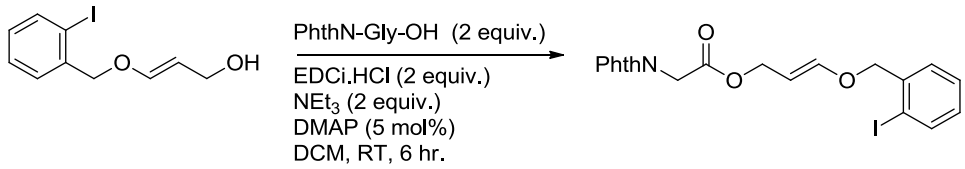
EDCi.HCl (2.23 g, 11.6 mmol), triethylamine (1.62 mL, 11.6 mmol), phthaloyl glycine **228** (2.39 g, 11.6 mmol), catalytic DMAP and (*E*)-3-(allyloxy)prop-2-enol **251** (0.67 g, 5.81 mmol) were combined according to general procedure 3 to afford the title compound as a yellow solid (1.24 g, 71%). MP: 73 -75 °C; FTIR (film/cm^{-1}) υ_{max}: 3077.4, 2981.4, 2946.5, 2888.4, 2867.7, 1776.6, 1746.6, 1722.0, 1671.7, 1654.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.26 (d, 2H, *J* = 5.1 Hz, $OCH_2CH{=}CH_2$), 4.42 (s, 2H, NCH_2CO_2), 4.59 (d, 2H, *J* = 8.0 Hz, $OCH_2CH{=}CHO$), 4.94 – 5.00 (m, 1H, $OCH_2CH{=}CHO$), 5.25 (d, 1H, *J* = 10.5 Hz, $OCH_2CH{=}CH_2$), 5.33 (d, 1H, *J* = 17.3 Hz, $OCH_2CH{=}CH_2$), 5.93 (ddt, 1H, *J* = 19.3, 10.6, 5.8 Hz, $OCH_2CH{=}CH_2$), 6.59 (d, 1H, *J* = 12. 6 Hz, $OCH_2CH{=}CHO$), 7.73 – 7.77 (m, 2H, Ar-*H* Phth), 7.86 – 7.91 (m, 2H, Ar-*H* Phth). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 64.2, 70.3, 97.7, 118.1, 123.6, 132.0, 132.6, 134.3, 152.8, 167.3, 167.5; HRMS (ESI, +ve) *m/z* calcd. for $C_{16}H_{15}NO_5Na$ 324.0845, found 324.0849 $(M+Na)^+$.

(*E*)-3-Benzyloxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate (265)



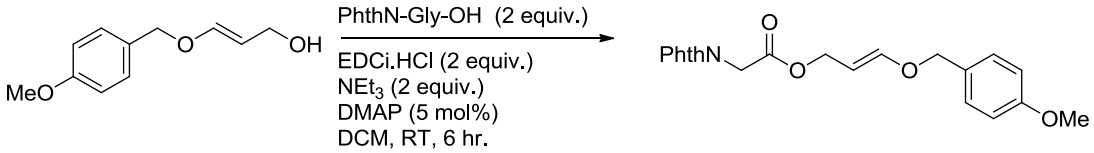
EDCi.HCl (2.12 g, 11.1 mmol), triethylamine (1.53 mL, 11.1 mmol), phthaloyl glycine **228** (2.26 g, 11.1 mmol), catalytic DMAP and (*E*)-3-(benzyloxy)prop-2-enol **252** (0.91 g, 5.53 mmol) were combined according to general procedure 3 to afford the title compound as a white solid (1.43 g, 74%). MP: 90 – 92 °C; FTIR (film/cm^{-1}) υ_{max}: 3035.3, 2936.1, 1777.4, 1744.2, 1716.1, 1651.8, 1614.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.44 (s, 2H, NCH_2CO_2), 4.62 (d, 2H, *J* = 8.0 Hz, $OCH_2CH{=}CHO$), 4.79 (s, 2H, OCH_2Ph), 5.07 (dt, 1H, *J* = 12.5, 8.0 Hz, $OCH_2CH{=}CHO$), 6.70 (d, 1H, *J* = 12.5 Hz, $OCH_2CH{=}CHO$), 7.31 – 7.40 (m, 5H, Ar-*H* Ph), 7.77 – 7.74 (m, 2H, Ar-*H* Phth), 7.88 – 7.91 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 64.2, 71.5, 97.9, 123.6, 123.6, 127.7, 128.2, 128.3, 128.5, 128.6, 128.7, 132.1, 136.2, 152.8, 167.3, 167.5; HRMS (ESI, +ve) *m/z* calcd. for $C_{20}H_{17}NO_5Na$ 374.1004, found 374.0998. $(M+Na)^+$.

(*E*)-3-(2-Iodobenzyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate (266)



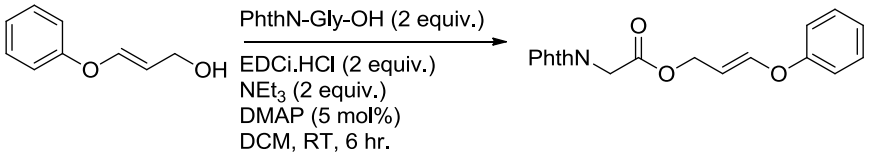
EDCi.HCl (1.15 g, 6.00 mmol), triethylamine (0.84 mL, 6.00 mmol), phthaloyl glycine **228** (1.23 g, 6.00 mmol), catalytic DMAP and (*E*)-3-(2-iodobenzyloxy)prop-2-enol **253** (0.88 g) were combined according to general procedure 3, to afford the title compound as a white solid. (1.00 g, 70%). MP: 82 – 84 °C; FTIR (film/cm^{-1}) υ_{max}: 3060.4, 2944.7, 2889.8, 1776.6, 1721.1, 1654.0, 1615.8; ^{1}H NMR (500 MHz, $CDCl_3$) 4.44 (s, 2H, NCH_2CO$_2$), 4.63 (d, 2H, *J* = 7.9 Hz, OCH_2CH=CHO), 4.76 (s, 2H, OCH_2Ar), 5.09 (dt, 1H, *J* = 12.8, 7.9 Hz, OCH$_2$C*H*=CHO), 6.71 (d, 1H, *J* = 12.8 Hz, OCH$_2$CH=C*H*O), 6.99 **–** 7.04 (m, 1H, Ar-*H* Ph), 7.41 **–** 7.33 (m, 2H, Ar-*H* Phth), 7.71 **–** 7.75 (m, 2H, Ar-*H* Phth), 7.82 **–** 7.84 (m, 1H, Ar-*H* Ph), 7.86 **–** 7.89 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 64.0, 75.1, 97.3, 98.4, 123.6, 128.4, 128.7, 129.7, 132.0, 134.2, 138.5, 139.3, 152.5, 167.3, 167.4; HRMS (ESI, +ve) *m/z:* calcd. for $C_{20}H_{16}INO_5Na$, 499.9971, found 499.9932 $(M+Na)^+$.

(*E*)-3-(4-Methoxybenzyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate (267)



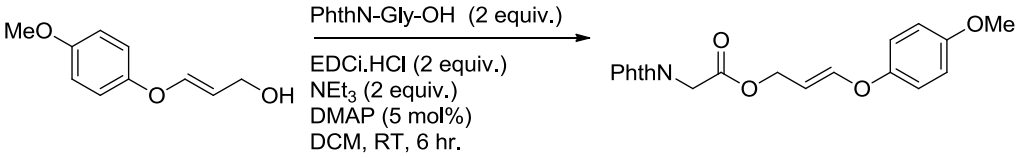
EDCi.HCl (1.53 g, 7.98 mmol), triethylamine (1.10 mL, 7.98 mmol), phthaloyl glycine **228** (1.66 g, 7.98 mmol), catalytic DMAP and (*E*)-3-(4-methoxybenzyloxy)prop-2-enol **254** (0.77 g, 3.99 mmol) were combined according to general procedure 3, to afford the title compound as a white solid. (0.76 g, 56%). MP: 72 – 76 °C; FTIR (film/cm^{-1}) υ_{max}: 3057.9, 3002.0, 2942.3, 2838.7, 1775.3, 1720.1, 1653.9, 1613.2: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.81 (s, 3H, ArOCH_3), 4.47 (d, 2H, *J* = 5.1 Hz, OCH_2Ar), 4.61 (d, 2H, *J* = 7.8 Hz, OCH_2CH=CHO), 4.71 (s, 2H, NCH_2CO$_2$), 5.05 (dt, 1H, *J* = 12.7, 7.8 Hz, OCH$_2$C*H*=CHO), 6.67 (d, 1H, *J* = 12.7 Hz, OCH$_2$CH=C*H*O), 6.90 (m, 2H, Ar-*H* Ph), 7.28 (m, 2H, Ar-*H* Ph), 7.73 **–** 7.76 (m, 2H, Ar-*H* Phth), 7.87 **–** 7.90 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 55.3, 64.3, 71.3, 97.8, 114.0, 123.6, 128.3, 129.4, 132.0, 134.2, 152.8, 159.6, 167.3, 167.5; HRMS (ESI, +ve) *m/z*: calcd. for $C_{21}H_{19}NO_6Na$ 404.1110, found 404.1076 $(M+Na)^+$.

(*E*)-3-(Phenyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate (268)



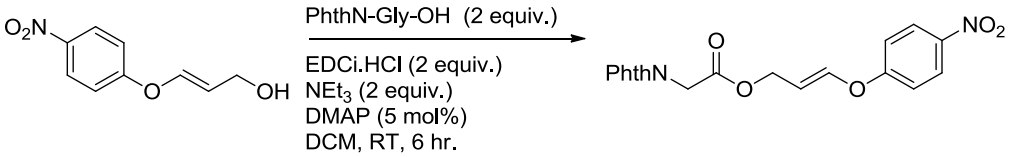
EDCi.HCl (1.53 g, 7.98 mmol), triethylamine (1.10 mL, 7.98 mmol), phthaloyl glycine **228** (1.64 g, 7.98 mmol), catalytic DMAP and (*E*)-3-(phenyloxy)prop-2-enol **255** (0.60 g, 3.99 mmol) were combined according to general procedure 3, to afford the title compound as a white solid. (1.10 g, 82%). MP: 124 - 127 °C; FTIR (film/cm^{-1}) υ_{max}: 3058.1, 2988.7, 2950.3, 1775.7, 1724.0, 1676.6, 1654.6, 1593.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.47 (s, 2H, NC*H*$_2$CO$_2$), 4.69 (d, 2H, *J* = 8.1 Hz, OC*H*$_2$CH=CHO), 5.45 (dt, 1H, *J* =12.1, 8.1 Hz, OCH$_2$C*H*=CHO), 6.81 (d, 1H, *J* = 12.1 Hz, OCH$_2$CH=C*H*O), 7.01 (d, 2H, *J* = 7.9 Hz, Ar-*H* Ph), 7.12 (t, 1H, *J* = 7.9 Hz, Ar-*H* Ph), 7.34 (t, 2H, *J* = 7.9 Hz, Ar-*H* Ph), 7.75 – 7.78 (m, 2H, Ar-*H* Phth), 7.89 – 7.82 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 63.1, 104.6, 117.2, 123.6, 129.7, 132.0 134.3, 149.0, 156.5, 167.2, 167.5; HRMS (ESI, +ve) *m/z*: calcd. for $C_{19}H_{15}NO_5Na$ 360.0848, found 360.0828 $(M+Na)^+$.

(*E*)-3-(4-Methoxyphenoxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate (269)



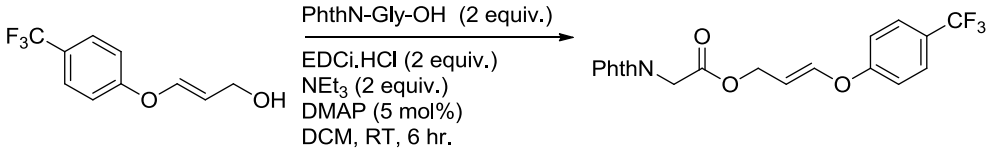
EDCi.HCl (1.35 g, 7.04 mmol), triethylamine (1.10 mL, 7.04 mmol), phthaloyl glycine **228** (1.44 g, 7.04 mmol), catalytic DMAP and (*E*)-3-(4-methoxyphenyloxy)prop-2-enol **256** (0.63 g, 3.52 mmol) were combined according to general procedure 3 , to afford the title compound as a yellow solid. (1.20 g, 77%). MP: 80 – 82 °C; FTIR (film/cm^{-1}) υ_{max}: 3063.9, 2945.9, 1776.6, 1749.7, 1723.4, 1675.4, 1613.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.74 (s, 3H, ArOC*H*$_3$), 4.42 (s, 2H, NC*H*$_2$CO$_2$), 4.63 (d, 2H, *J* = 8.2 Hz, OC*H*$_2$CH=CHO), 5.30 (dt, 1H, *J* = 12.1, 8.2 Hz, OCH$_2$C*H*=CHO), 6.71 (d, 1H, *J* = 12.1 Hz, OCH$_2$CH=C*H*O), 6.82 (m, 2H, Ar-*H* Ph), 6.90 (m, 2H, Ar-*H* Ph), 7.69 – 7.73 (m, 2H, Ar-*H* Phth), 7.83 – 7.86 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.9, 39.0, 53.5, 55.6, 63.2, 103.3, 114.7, 118.7, 123.6, 132.0, 134.2, 150.3, 155.9, 167.2, 167.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{20}H_{17}NO_6Na$ 360.0954, found 390.0954 $(M+Na)^+$.

(*E*)-3-(4-Nitrophenoxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate (270)



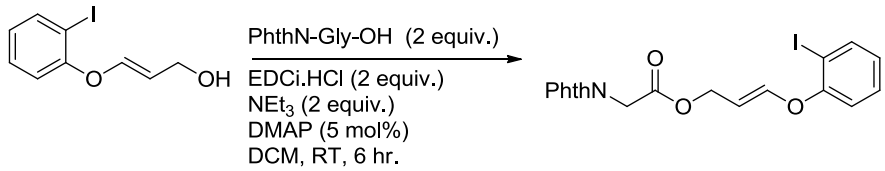
EDCi.HCl (1.17 g, 6.10 mmol), triethylamine (0.80 mL, 6.10 mmol), phthaloyl glycine **228** (1.17 g, 6.10 mmol), catalytic DMAP and (*E*)-3-(4-nitrophenyloxy)prop-2-enol **257** (0.60 g, 3.05 mmol) were combined according to general procedure 3, to afford the title compound as a yellow solid. (0.75 g, 69%). MP: 80 – 82 °C; FTIR (film/cm^{-1}) υ_{max}: 3087.3, 3006.6, 2965.3, 2921.2, 1774.0, 1702.3, 1654.2, 1774.0, 1702.3, 1654.2, 1591.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.49 (s, 2H, NC*H*$_2$CO$_2$), 4.74 (d, 2H, *J* = 7.7 Hz, OC*H*$_2$CH=CHO), 5.65 (dt, 1H, *J* = 12.1, 7.7 Hz, OCH$_2$C*H*=CHO), 6.84 (d, 1H, *J* = 12.1 Hz, OCH$_2$CH=C*H*O), 7.08 – 7.11 (m, 2H, Ar-*H* Ph), 7.76 –7.80 (m, 2H, Ar-*H* Phth), 7.90 – 7.93 (m, 2H, Ar-*H* Phth), 8.23 – 8.27 (m, 2H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 62.1, 108.8, 116.6, 123.7, 126.0, 132.0, 134.3, 143.4, 146.1, 161.1, 167.2, 167.4; HRMS (ESI, +ve) *m/z: calcd*. for $C_{19}H_{14}N_2O_7Na$ 405.0699, found 405.0689 $(M+Na)^+$.

(*E*)-3-(4-Trifluoromethylphenyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate (271)



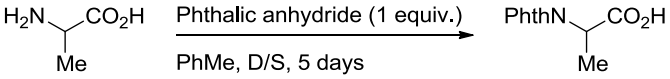
EDCi.HCl (0.88 g, 4.59 mmol), triethylamine (0.64 mL, 4.59 mmol), phthaloyl glycine **228** (0.94 g, 4.59 mmol), catalytic DMAP and (*E*)-3-(4-trifluoromethylphenyloxy)prop-2-enol **258** (0.50 g, 2.30 mmol) were combined according to general procedure 3, to afford the title compound as an off-white solid. (0.68 g, 73%). MP: 114 – 115 °C; FTIR (film/cm^{-1}) υ_{max}: 3078.4, 2948.1, 1777.3, 1750.8, 1724.0, 1677.7, 1613.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.48 (s, 2H, NC*H*$_2$CO$_2$), 4.72 (d, 2H, *J* = 8.0 Hz, OC*H*$_2$CH=CHO), 5.56 (dt, 1H, *J* = 12.4, 8.0 Hz, OCH$_2$C*H*=CHO), 6.81 (d, 1H, *J* = 12.4 Hz, OCH$_2$CH=C*H*O), 7.09 (m, 2H, Ar-*H* Ph), 7.61 (m, 2H, Ar-*H* Ph), 7.76 – 7.79 (m, 2H, Ar-*H* Phth), 7.89 – 7.93 (m, 2H Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 62.5, 106.9, 116.9, 121.9, 123.7, 127.2 (q, *J* = 3.6 Hz), 132.0, 134.3, 134.5, 147.3, 158.9, 167.2, 167.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{20}H_{14}F_3NO_5Na$ 428.0722, found 428.0700 $(M+Na)^+$.

(*E*)-3-(2-Iodophenyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate (272)



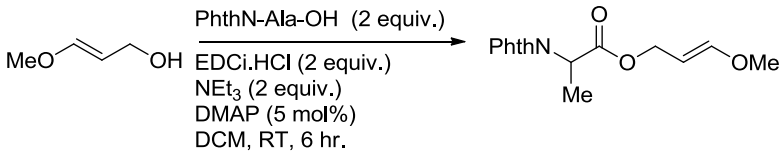
EDCi.HCl (1.39 g, 7.25 mmol), triethylamine (1.00 mL, 7.25 mmol), phthaloyl glycine **228** (1.50 g, 7.25 mmol), catalytic DMAP and (*E*)-3-(4-methoxybenzyloxy)prop-2-enol **259** (1.00 g, 3.63 mmol) were combined according to general procedure 3, to afford the title compound as a cream solid. (1.22 g, 73%). MP: 81 – 85 °C; FTIR (film/cm^{-1}) υ_{max}: 3061.8, 2945.2, 1776.0, 1748.4, 1723.5, 1673.7, 1615.2, 1579.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.45 (s, 2H, NC*H*$_2$CO$_2$), 4.67 (d, 2H, *J* = 7.7 Hz, OC*H*$_2$CH=CHO), 5.44 (dt, 1H, *J* = 12.2, 7.7 Hz, OCH$_2$C*H*=CHO), 6.71 (d, 1H, *J* = 12.2 Hz, OCH$_2$CH=C*H*O), 6.84 (t, 1H, *J* = 8.1 Hz, Ar-*H* Ph), 6.95 (d, 1H, *J* = 8.1 Hz, Ar-*H* Ph), 7.30 (t, 1H, *J* = 8.1 Hz, Ar-*H* Ph), 7.71 **–** 7.74 (m, 2H, Ar-*H* Phth), 7.77 (dd, 1H, *J* = 8.1, 1.4 Hz, Ar-*H* Ph), 7.84 **–** 7.88 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 62.7, 87.2, 105.7, 117.5, 123.6, 125.6, 129.7, 132.0, 134.3, 139.8, 148.5, 155.6, 167.2, 167.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{19}H_{14}INO_5Na$ 485.9814, found 485.9778 $(M+Na)^+$.

2-(1,3-dioxoisoindolin-2-yl)propanoic acid (260)



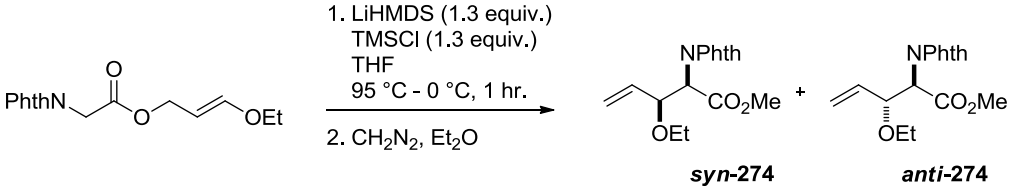
DL-alanine (1.00 g, 11.2 mmol, 1 equiv.) and phthalic anhydride (1.66 g, 11.2 mmol, 1 equiv.) were refluxed in toluene (50 mL) under Dean-Stark conditions for 5 days, cooled and solvent removed *in vacuo* to afford a white solid. Purification was achieved by recystallisation from water to afford the title compound as white needles. (1.80 g, 73%). MP: 165 – 167 °C, Lit: 162.5 – 163 °C;[165] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.68 (d, 3H, *J* = 7.5 Hz, NCH(C*H*$_3$)CO$_2$H), 4.90 (br, 1H, CO$_2$*H*), 4.97 (q, 1H, *J* = 7.5 Hz, NC*H*(CH$_3$)CO$_2$H), 7.85 – 7.81 (m, 2H, Ar-*H* Phth), 7.90 – 7.87 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 47.2, 122.9, 131.8, 134.2, 167.6, 171.8. All analytical data is in accordance with reported literature values.[166]

(*E*)-3-Methoxyallyl 2-(1,3-dioxoisodolin-2-yl)propanote (273)



EDCi.HCl (1.23 g, 6.43 mmol), triethylamine (0.77 mL, 6.43 mmol), 2-(1,3-diocoisoindoin-2-yl)propanoic acid **260** (1.23 g, 6.43 mmol), catalytic DMAP and (*E*)-3-(methoxy)prop-2-enol **224** (0.25 g, 3.21 mmol) were combined according to general procedure 3, to afford the title compound as a colourless oil. (0.78 g, 95%). FTIR (film/cm^{-1}) υ_{max}: 2997.5, 2944.0, 1780.1, 1713.9, 1654.1, 1612.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.68 (d, 3H, *J* = 7.3 Hz, NCH(C*H*$_3$)CO$_2$), 3.53 (s, 3H, OC*H*$_3$), 4.53 – 4.60 (m, 2H, OC*H*$_2$CH=CHO), 4.87 (dt, 1H, *J* = 13.1, 7.6 Hz, OCH$_2$C*H*=CHO), 4.94 (q, 1H, *J* = 7.3 Hz, NC*H*(CH$_3$)CO$_2$), 6.59 (d, 1H, *J* = 13.1 Hz, OCH$_2$CH=C*H*O), 7.71 – 7.74 (m, 2H, Ar-*H* Phth), 7.83 – 7.87 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.2, 27.6, 47.6, 47.7, 53.4, 56.1, 64.1, 96.5, 123.5, 131.9, 132.0, 134.1, 153.7, 167.5, 169.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_{15}H_{15}NO_5Na$ 312.0837, found 312.0848 $(M+Na)^+$.

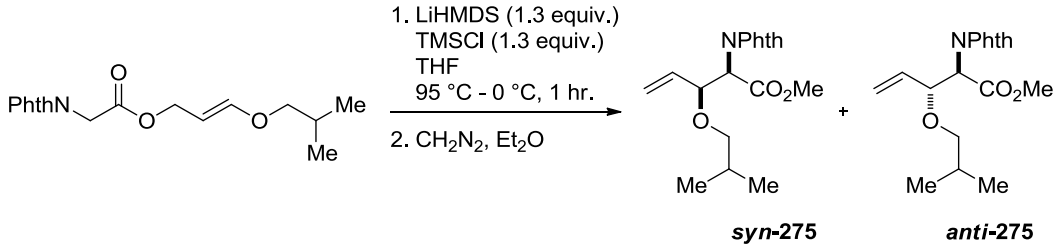
(±)-(*2R,3R*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-ethoxypent-4-enoate (274)



(*E*)-3-Ethoxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate **261** (0.206 g, 0.71 mmol, 1 equiv.), TMSCl (0.11 mL, 0.92 mmol, 1.3 equiv.) and LiHMDS (0.85 mL, 0.85 mmol, 1.3 equiv.) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a yellow oil. (0.17 g, 79%, dr 9:1). FTIR (film/cm^{-1}) υ_{max}: 3062.5, 2977.4, 2955.5, 2928.3, 2896.7, 1778.0, 1753.4, 1719.1, 1672.1, 1612.4; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 0.94 (t, 3H, *J* = 7.0 Hz, OCH$_2$C*H*$_3$), 3.30 – 3.24 (m, 1H, OC*H*$_2$CH$_3$), 3.57 – 3.50 (m, 1H, OC*H*$_2$CH$_3$), 3.72 (s, 3H, CO$_2$C*H*$_3$), 4.63 (app. t, 1H, *J* = 7.1 Hz, CH$_2$=CHC*H*O), 4.86 (d, 1H, *J* = 7.1 Hz, NC*H*CO$_2$), 5.33 (d, 1H, *J* = 10.5 Hz, C*H*$_2$=CHCHO), 5.43 (d, 1H, *J* = 17.2 Hz, C*H*$_2$=CHCHO), 5.91 (ddd, 1H, *J* = 17.2, 10.5, 7.1 Hz, CH$_2$=C*H*CHO), 7.72 – 7.76 (m, 2H, Ar-*H* Phth), 7.86 – 7.89 (m, 2H, Ar-*H* Phth); *anti* δ: 1.20 (t, 3H, *J* = 7.9 Hz, OCH$_2$C*H*$_3$), 3.30 – 3.24 (m, 1H, OC*H*$_2$CH$_3$), 3.62–3.57 (m, 1H, OC*H*$_2$CH$_3$), 3.75 (s, 3H, CO$_2$C*H*$_3$), 4.65 (app. t, 1H, *J* = 7.1 Hz, CH$_2$=CHC*H*O), 4.89 (d, 1H, *J* = 7.1 Hz, NC*H*CO$_2$), 5.11 (d, 1H, *J* = 10.5 Hz,

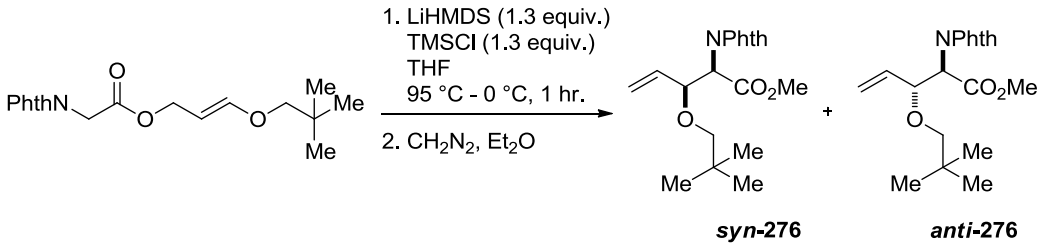
CH_2=CHCHO), 5.23 (d, 1H, *J* = 17.2 Hz, CH_2=CHCHO), 5.63 (ddd, 1H, *J* = 17.2, 10.5, 7.1 Hz, CH_2=C*H*CHO), 7.72 – 7.76 (m, 2H, Ar-*H* Phth), 7.86 – 7.89 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 15.0, 52.5, 55.9, 64.4, 76.2, 119.1, 123.5, 131.8, 134.1, 135.8, 167.5, 167.9; *anti* δ: 15.2, 52.6, 54.2, 64.7, 78.5, 120.0, 123.6, 131.7, 134.2, 134.5, 167.1, 168.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{18}NO_5$ 304.1185, found 304.1204 $(M+H)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-isobutoxypent-4-enoate (275)



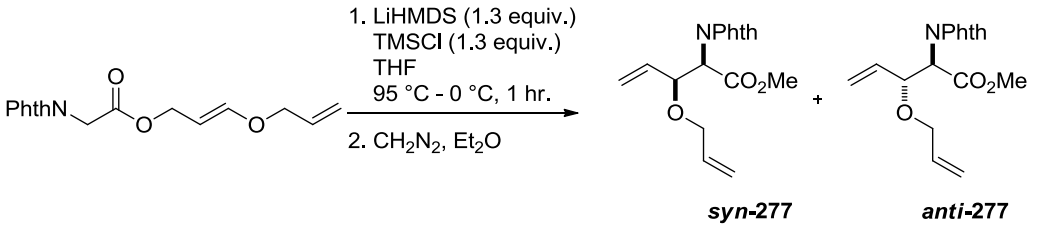
(*E*)-3-Isobutoxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate **262** (0.13 g, 0.40 mmol, 1 equiv.), TMSCl (0.07 mL, 0.51 mmol, 1.3 equiv.) and LiHMDS (0.47 mL, 0.47 mmol, 1.3 equiv.) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.09 g, 64%, dr 18:1). FTIR (film/cm^{-1}) υ_{max}: 2956.5, 2921.7, 2878.8, 1777.9, 1750.0, 1718.8, 1644.1; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 0.63 (dd, 6H, *J* = 19.0, 6.9 Hz, (CH_3)$_2$CHCH_2O), 1.60 (oct, 1H, *J* = 7.0 Hz, (CH_3)$_2$C*H*CH_2O), 2.89 (dd, 1H, *J* = 7.0, 2.5 Hz, (CH_3)$_2$CHCH_2O), 3.30 (dd, 1H, *J* = 6.2, 2.5 Hz, (CH_3)$_2$CHCH_2O), 3.73 (s, 3H, CO_2CH_3), 4.58 (app. t, *J* = 9.1 Hz, CH_2=CHC*H*O), 4.87 (d, 1H, *J* = 9.1 Hz, NC*H*CO_2), 5.35 (d, 1H, *J* = 10.7 Hz, CH_2=CHCHO), 5.44 (d, 1H, *J* = 17.4 Hz, CH_2=CHCHO), 5.90 (ddd, 1H, *J* = 17.4, 10.7, 9.1 Hz, CH_2=C*H*CHO), 7.73 – 7.76 (m, 2H, Ar-*H* Phth), 7.86 – 7.90 (m, 2H, Ar-*H* Phth); *anti* δ: 0.91 (dd, 6H, *J* = 7.8, 6.7 Hz, (CH_3)$_2$CHCH_2O), 1.86 (oct, 1H, *J* = 6.7 Hz, (CH_3)$_2$C*H*CH_2O), 2.89 (dd, 1H, *J* = 6.7, 2.0 Hz, (CH_3)$_2$CHCH_2O), 3.30 (dd, 1H, *J* = 6.7, 2.5 Hz, (CH_3)$_2$CHCH_2O), 3.76 (s, 3H, CO_2CH_3), 4.64 (app. t, 1H, *J* = 8.8 Hz, CH_2=CHC*H*O), 4.92 (d, 1H, *J* = 6.1 Hz, NC*H*CO_2), 5.12 (d, 1H, *J* = 10.1 Hz, CH_2=CHCHO), 5.23 (d, 1H, *J* = 17.2 Hz, CH_2=CHCHO), 5.62 (ddd, 1H, *J* = 17.2, 10.1, 6.1 Hz, CH_2=C*H*CHO), 7.73 – 7.76 (m, 2H, Ar-*H* Phth), 7.86 – 7.90 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 19.0, 28.3, 52.5, 55.8, 75.6, 76.5, 119.3, 123.4, 131.9, 134.1, 135.8, 167.5, 167.9; HRMS (ESI, +ve) *m/z*: calcd. for $C_{18}H_{21}NO_5Na$ 354.1317, found 354.1318 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(neopentyloxy)pent-4-enoate (276)



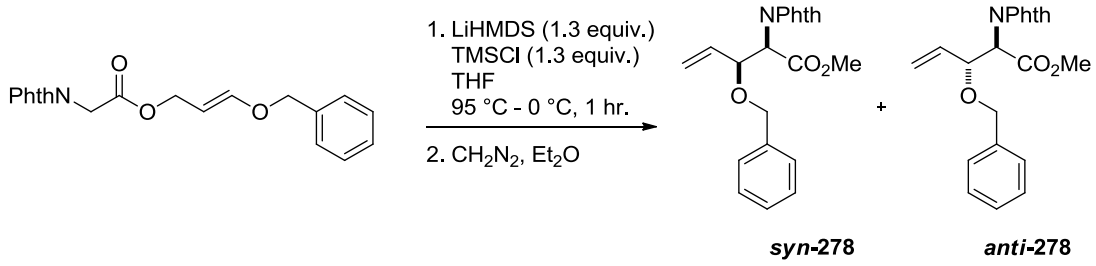
(*E*)-3-(Neopentyl)oxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate **263** (0.18 g, 0.53 mmol, 1 equiv.), TMSCl (0.09 mL, 0.69 mmol, 1.3 equiv.) and LiHMDS (0.64 mL, 0.64 mmol, 1.3 equiv.) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.14 g, 78%, dr 13:1). FTIR (film/cm^{-1}) υ_{max}: 3087.0, 2955.9, 2901.7, 2868.5, 1778.2, 1719.2, 1645.5, 1614.5; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 0.62 (s, 9H, $(CH_3)_3CCH_2O$), 2.75 (d, 1H, *J* = 8.6 Hz, $(CH_3)_3CCH_2O$), 3.15 (d, 1H, *J* = 8.6 Hz, $(CH_3)_3CCH_2O$), 3.71 (s, 3H, CO_2CH_3), 4.53 – 4.57 (m, 1H, CH_2=CHC*H*O), 4.86 (d, 1H, *J* = 10.3 Hz, NC*H*CO_2), 5.32 – 5.35 (m, 1H, CH_2=CHCHO), 5.43 (dt, 1H, *J* = 17.1, 1.5 Hz, CH_2=CHCHO), 5.88 (ddd, 1H, *J* = 17.1, 10.3, 6.7 Hz, CH_2=C*H*CHO), 7.71 – 7.74 (m, 2H, Ar-*H* Phth), 7.83 – 7.88 (m, 2H, Ar-*H* Phth); *anti* δ: 0.89 (s, 9H, $(CH_3)_3CCH_2O$), 2.89 (d, 1H, *J* = 8.3 Hz, $(CH_3)_3CCH_2O$), 3.29 (d, 1H, *J* = 8.3 Hz, $(CH_3)_3CCH_2O$), 3.74 (s, 3H, CO_2CH_3), 4.62 (app. t, 1H, *J* = 8.6 Hz, CH_2=CHC*H*O), 4.92 (d, 1H, *J* = 8.6 Hz, NC*H*CO_2), 5.09 – 5.12 (m, 1H, CH_2=CHCHO), 5.20 – 5.24 (m, 1H, CH_2=CHCHO), 5.60 (ddd, 1H, *J* = 17.5, 10.3, 8.6 Hz, CH_2=C*H*CHO), 7.71 – 7.74 (m, 2H, Ar-*H* Phth), 7.83 – 7.88 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 26.4, 31.6, 52.4, 55.7, 76.3, 79.2, 119.1, 123.4, 131.9, 134.1, 135.8, 167.4, 167.9; *anti* δ: 26.7, 31.9, 52.5, 54.5, 78.8, 79.6, 119.8, 123.6, 131.7, 134.2, 134.6, 167.2, 168.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{19}H_{24}NO_5$ 346.1654, found 346.1645 $(M+H)^+$.

(±)-(1*R*,2*R*)-2-(allyloxy)-1-(1,3-dioxoisoindolin-2-yl)but-3-enyl acetate (277)



(*E*)-3-(Allyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate **264** (0.24 g, 0.78 mmol, 1 equiv.), TMSCl (0.13 mL, 1.01 mmol, 1.3 equiv.) and LiHMDS (0.93 mL, 0.93 mmol, 1.3 equiv.) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (4:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.17 g, 70%, dr 10:1). FTIR (film/cm^{-1}) υ_{max}: 3082.3, 2985.4, 2954.3, 2921.8, 2865.3, 1777.8, 1750.0, 1718.6, 1646.1, 1613.0; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* and *anti* δ: 3.72 (s, 3H), 4.96 – 4.90 (m, 1H), 4.97 (dq, 1H, *J* = 10.5, 1.7 Hz), 5.07 (dq, 1H, *J* = 17.2, 2.1 Hz), 5.38 (dt, 1H, *J* = 10.8, 0.91 Hz), 5.15 – 5.33 (m, 1H), 5.45 (dt, 1H, *J* = 17.1, 1.4 Hz), 5.62 – 5.71 (m, 1H), 5.91 (ddd, 1H, *J* = 17.1, 10.6, 6.9 Hz), 7.73 – 7.76 (m, 2H), 7.86 – 7.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 52.5, 55.7, 69.5, 75.9, 116.6, 119.7, 123.5, 131.9, 134.1, 134.3, 135.3, 167.4, 167.8; *anti* δ: 52.7, 54.2, 70.1, 78.1, 117.1, 120.5, 123.6, 131.7, 134.2, 135.3, 167.1, 168.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{17}H_{17}NO_5Na$ 338.1004, found 338.0980 $(M+Na)^+$.

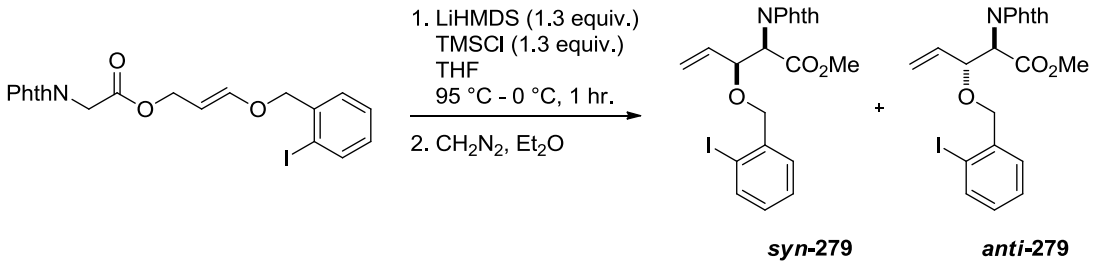
(±)-(*2R,3R*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-benzyloxypent-4-enoate (278)



(*E*)-3-(Benzyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate **265** (0.13 g, 0.37 mmol, 1 equiv.), TMSCl (0.06 mL, 0.48 mmol, 1.3 equiv.) and LiHMDS (0.44 mL, 0.44 mmol, 1.3 equiv) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.10 g, 70%, dr 10:1). FTIR (film/cm^{-1}) υ_{max}: 3035.8, 2999.3, 2954.3, 2839.3, 1749.8, 1718.9, 1645.5; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 3.72 (s, 3H, CO_2CH_3), 4.47 – 4.61 (m, 2H, OCH_2Ph), 4.73 (app. t, 1H, *J* = 8.6 Hz, CH_2=CHC*H*O), 4.93 (d, 1H, *J* = 8.6 Hz, NC*H*CO_2), 5.41 – 5.43 (m, 1H, CH_2=CHCHO), 5.49 – 5.53 (m, 1H, CH_2=CHCHO), 5.98 (ddd, 1H, *J* = 17.3, 10.7, 8.6

Hz, CH_2=C*H*CHO), 7.05 – 7.15 (m, 5H, Ar-*H* Ph), 7.73 – 7.75 (m, 2H, Ar-*H* Phth), 7.83 – 7.87 (m, 2H, Ar-*H* Phth); *anti* δ: 3.76 (s, 3H, CO_2CH_3), 4.61 – 4.47 (m, 2H, OCH_2Ph), 4.81 (app. t, 1H, *J* = 8.4 Hz, CH_2=CHC*H*O), 5.01 (d, 1H, *J* = 8.4 Hz, NC*H*CO_2), 5.18 – 5.21 (m, 1H, C*H*$_2$=CHCHO), 5.28 – 5.32 (m, 1H, C*H*$_2$=CHCHO), 5.71 (ddd, 1H, *J* = 17.3, 10.7, 8.4 Hz, CH_2=C*H*CHO), 7.34 – 7.38 (m, 5H, Ar-*H* Ph), 7.73 – 7.75 (m, 2H, Ar-*H* Phth), 7.83 – 7.87 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 38.8, 52.5, 55.7, 70.6, 76.2, 123.5, 127.5, 128.1, 128.3, 128.7, 131.9, 134.0, 135.3, 167.4, 167.7; *anti* δ: 39.0, 52.7, 54.3, 67.6, 77.4, 123.7, 127.3, 128.0, 128.3, 128.5, 132.0, 134.3, 137.8, 167.2, 167.5; HRMS (ESI, +ve) *m/z*: calcd. for $C_{21}H_{19}NO_5Na$ 388.1161, found 388.1168 $(M+Na)^+$.

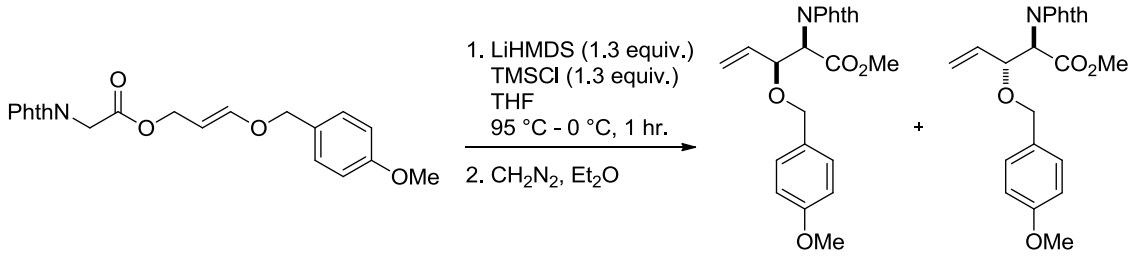
(±)-(2*R*,3*S*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(2-iodobenzyloxy)pent-4-enoate (279)



(*E*)-3-(2-Iodobenzyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate **266** (0.25 g, 0.51 mmol, 1 equiv.), TMSCl (0.08 mL, 0.66 mmol, 1.3 equiv.) and LiHMDS (0.61 mL, 0.61 mmol, 1.3 equiv) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.12 g, 50%, dr 14:1). FTIR (film/cm^{-1}) υ_{max}: 3063.2, 2953.1, 1777.1, 1751.6, 1719.5, 1642.4, 1613.1, 1587.7, 1565.5; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 3.72 (s, 3H, CO_2CH_3), 4.47 – 4.56 (m, 2H, OCH_2Ar), 4.80 (app. t, 1H, *J* = 8.9 Hz, CH_2=CHC*H*O), 4.98 (d, 1H, *J* = 8.9 Hz, NC*H*CO_2), 5.45 (app. d, 1H, *J* = 17.1 Hz, C*H*$_2$=CHCHO), 5.56 (dt, 1H, *J* = 17.2, 1.8 Hz, C*H*$_2$=CHCHO), 6.00 (ddd, 1H, *J* = 17.2, 10.5, 8.9 Hz, CH_2=C*H*CHO), 6.86 (td, 1H, *J* = 7.8, 1.5 Hz, Ar-*H* Ph), 7.13 (td, 1H, *J* = 7.8, 1.5 Hz, Ar-*H* Ph), 7.19 (dd, 1H, *J* = 7.8, 1.5 Hz, Ar-*H* Ph), 7.64 (dd, 1H, *J* = 7.8, 1.5 Hz, Ar-*H* Ph), 7.72 – 7.75 (m, 2H, Ar-*H* Phth), 7.83 – 7.86 (m, 2H, Ar-*H* Phth); *anti* δ: 3.76 (s, 3H, CO_2CH_3), 4.59 – 4.62 (m, 2H, OCH_2Ar), 4.88 (app. t, 1H, *J* = 8.2 Hz, CH_2=CHC*H*O), 5.06 (d, 1H, *J* = 8.2 Hz, NC*H*CO_2), 5.22 (app. d, 1H, *J* = 10.2 Hz, C*H*$_2$=CHCHO), 5.35 (app. d, 1H, *J* = 17.1 Hz, C*H*$_2$=CHCHO), 5.74 (ddd, 1H, *J* = 17.1, 10.2, 8.1 Hz, CH_2=C*H*CHO), 6.86 (td, 1H, *J* = 7.7, 1.5 Hz, Ar-*H*

Ph), 7.13 (td, 1H, *J* = 7.7, 1.5 Hz, Ar-*H* Ph), 7.19 (dd, 1H, *J* = 7.7, 1.5 Hz, Ar-*H* Ph), 7.64 (dd, 1H, *J* = 7.7, 1.5 Hz, Ar-*H* Ph), 7.75 – 7.77 (m, 2H, Ar-*H* Phth), 7.92 – 7.98 (m, 2H, Ar-*H* Phth);^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 38.8, 52.6, 74.2, 76.4, 123.5, 128.0, 128.8, 129.0, 131.9, 134.1, 134.3, 134.9, 138.9, 167.3, 167.6; *anti* δ: 38.9, 52.7, 74.9, 78.9, 123.6, 128.4, 129.0, 129.1, 132.0, 133.8, 137.5, 139.6, 140.1, 167.4, 167.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_{21}H_{18}NO_5Na$ 514.0127, found 514.0122 $(M+Na)^+$.

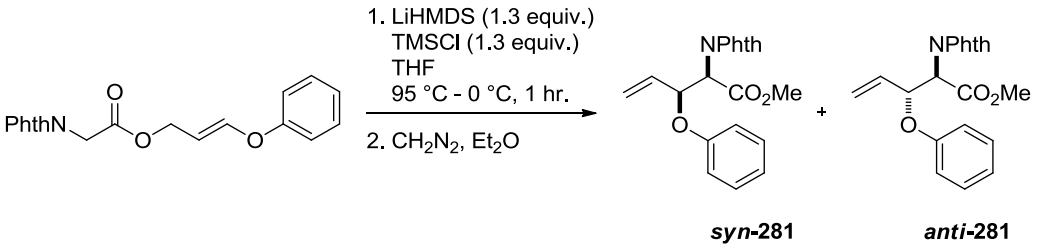
(±)-(2*R*,3*S*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(4-methoxybenyloxy)pent-4-enoate (280)



***syn*-280** ***anti*-280**

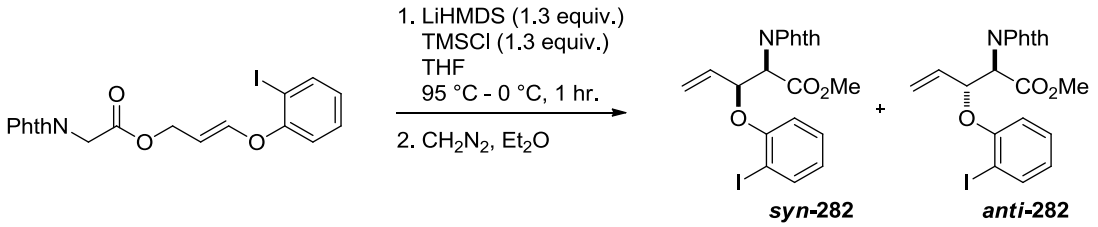
(*E*)-3-(4-Methoxybenzyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate **267** (0.13 g, 0.34 mmol), TMSCl (0.06 mL, 0.44 mmol) and LiHMDS (0.40 mL, 0.40 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.08 g, 63%, dr 8:1). FTIR (film/cm^{-1}) υ_{max}: 3064.0, 3001.2, 2954.3, 2838.6, 1777.1, 1749.0, 1720.0, 1642.9, 1613.2, 1586.4; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 3.71 (s, 3H, ArOCH_3), 3.72 (s, 3H, CO_2CH_3), 4.46 – 4.51 (m, 2H, OCH_2Ar), 4.70 (app. t, 1H, *J* = 8.4 Hz, CH_2=CHC*H*O), 4.90 (d, 1H, *J* = 8.4 Hz, NC*H*CO_2), 5.41 (d, 1H, *J* = 10.2 Hz, CH_2=CHCHO), 5.50 (d, 1H, *J* = 17.0 Hz, CH_2=CHCHO), 5.98 (ddd, 1H, *J* = 17.0, 10.2, 8.4 Hz, CH_2=C*H*CHO), 6.62 (m, 2H, Ar-*H* Ph), 6.97 (m, 2H, Ar-*H* Ph), 7.72 – 7.78 (m, 2H, Ar-*H* Phth), 7.86 – 7.81 (m, 2H, Ar-H Phth); *anti* δ: 3.71 (s, 3H, ArOCH_3), 3.72 (s, 3H, CO_2CH_3), 4.46 – 4.51 (m, 2H, OCH_2Ar), 4.78 (app. t, 1H, *J* = 8.4 Hz, CH_2=CHC*H*O), 4.99 (d, 1H, *J* = 8.4 Hz, NC*H*CO_2), 5.18 (d, 1H, *J* = 10.1 Hz, CH_2=CHCHO), 5.28 (d, 1H, *J* = 17.9 Hz, CH_2=CHCHO), 5.70 (ddd, 1H, *J* = 17.9, 10.1, 8.4 Hz, CH_2=C*H*CHO), 6.62 (m, 2H, Ar-*H* Ph), 6.89 (m, 2H, Ar-*H* Ph), 7.72 – 7.77 (m, 2H, Ar-*H* Phth), 7.88 – 7.91 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 52.5, 55.1, 55.7, 70.3, 75.8, 113.5, 114.0, 119.6, 123.4, 129.2, 130.3, 131.9, 134.0, 158.9, 167.3, 167.8; *anti* δ: 52.7, 54.2, 55.3, 71.0, 78.4, 113.8, 113.9, 120.5, 123.6, 129.6, 130.0, 132.0, 134.2, 159.9, 167.5, 168.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{22}H_{21}NO_5Na$ 396.1447, found 418.1283 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-phenoxypent-4-enoate (281)



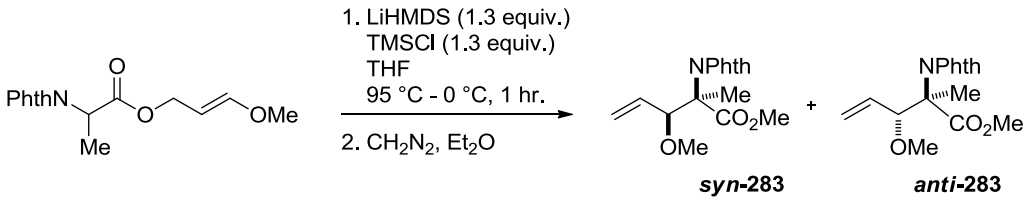
(*E*)-3-(4-Phenyloxybenzyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate **268** (0.11 g, 0.33 mmol, 1 equiv.), TMSCl (0.06 mL, 0.43 mmol, 1.3 equiv.) and LiHMDS (0.40 mL, 0.40 mmol, 1.3 equiv) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.10 g, 81%, dr 14:1). FTIR (film/cm^{-1}) υ_{max}: 3864.2, 3848.9, 2954.0, 2849.6, 1727.4, 1750.6, 1720.2, 1646.5, 1596.0; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 3.76 (s, 3H, CO_2CH_3), 5.10 (d, 1H , *J* = 5.6 Hz, CH_2=CHC*H*O), 5.36 (d, 1H, *J* = 5.6 Hz, NC*H*CO_2), 5.50 (d, 1H, *J* = 17.2 Hz, C*H*$_2$=CHCHO), 5.57 (app. t, 1H, *J* = 8.6 Hz, C*H*$_2$=CHCHO), 6.17 (ddd, 1H, *J* = 17.2, 10.6, 5.6 Hz, CH_2=C*H*CHO), 6.80 **–** 7.17 (m, 5H, Ar-*H* Ph), 7.72 **–** 7.78 (m, 2H, Ar-*H* Phth), 7.84 **–** 7.87 (m, 2H, Ar-*H* Phth); *anti* δ: 3.78 (s, 3H, CO_2CH_3), 5.19 (t, 1H , *J* = 8.0 Hz, CH_2=CHC*H*O), 5.34 (d, 1H, *J* = 10.6 Hz, NC*H*CO_2), 5.42 **–** 5.46 (m, 2H, C*H*$_2$=CHCHO), 5.79 **–** 5.86 (m, 1H, CH_2=C*H*CHO), 6.80 - 7.17 (m, 5H, Ar-*H* Ph), 7.72 **–** 7.78 (m, 2H, Ar-*H* Phth), 7.84 **–** 7.87 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 39.0, 52.7, 55.7, 75.0, 116.4, 119.6, 123.7, 129.7, 131.7, 134.2, 149.0, 157.4, 167.3, 167.5; *anti* δ: 39.1, 52.9, 54.3, 63.1, 117.2, 121.7, 123.7, 129.5, 132.0, 134.3, 150.3, 156.5, 167.2, 167.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{20}H_{17}NO_5Na$ 374.1004, found 374.0995 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(2-iodophenoxy)pent-4-enoate (282)



(*E*)-3-(2-Iodophenyloxy)allyl 2-(1,3-dioxoisoindolin-2-yl)acetate **272** (0.11 g, 0.22 mmol, 1 equiv.), TMSCl (0.04 mL, 0.29 mmol, 1.3 equiv.) and LiHMDS (0.27 mL, 0.27 mmol, 1.3 equiv) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) afforded the title compond as a colourless oil. (0.05 g, 50%, dr 17:1). FTIR (film/cm^{-1}) υ_{max}: 3090.3, 3060.4, 2954.3, 2923.8, 2846.3, 1777.7, 1750.1, 1719.7, 1611.0, 1581.6; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* and *anti* δ: (s, 3H, CO_2CH_3), 5.19 (d, 1H, *J* = 9.5 Hz, CH_2=CHC*H*O), 5.41 (d, 1H, *J* = 10.7 Hz, NC*H*CO_2), 5.51 (d, 1H, *J* = 17.7 Hz, CH_2=CHCHO), 5.68 (dd, 1H, *J* = 10.7, 4.4 Hz, CH_2=CHCHO), 6.24 (ddd, 1H, *J* = 17.7, 10.7, 9.5 Hz, CH_2=C*H*CHO), 6.64 (t, 1H, *J* = 7.7 Hz, Ar-*H* Ph), 6.84 (d, 1H, *J* = 7.7 Hz, Ar-*H* Ph), 7.21 (app. t, 1H, *J* = 7.7 Hz, Ar-*H* Ph), 7.60 (app. d, 1H, *J* = 7.7 Hz, Ar-*H* Ph), 7.72 – 7.76 (m, 2H, Ar-*H* Phth), 7.85 – 7.88 (m, 2H, Ar-*H* Phth);^{13}C NMR (125 MHz, $CDCl_3$) *syn* and *anti* δ: 52.8, 55.4, 74.7, 86.5, 113.9, 120.2, 123.0, 123.7, 129.2, 132.1, 134.1, 134.2, 139.4, 155.6, 167.3, 167.5; HRMS (ESI, +ve) *m/z*: calcd. for $C_{20}H_{16}INO_5Na$ 499.9971, found 499.9968 $(M+Na)^+$.

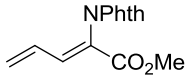
(±)-(2*S*,3*R*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)-3-methoxy-2-methylpent-4-enoate (283)



(*E*)-3-Methoxyallyl 2-(1,3-dioxoisodolin-2-yl)propanote **273** (0.22 g, 0.74 mmol, 1 equiv.), TMSCl (0.12 mL, 0.96 mmol, 1.3 equiv.) and LiHMDS (0.89 mL, 0.89 mmol, 1.3 equiv) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.16 g, 71%, dr 24:1). FTIR (film/cm^{-1}) υ_{max}: 3082.2, 2990.9, 2950.5, 2826.4, 1781.6, 1718.2, 1639.6, 1612.5; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 1.84 (s, 3H, NC(CH_3)CO_2), 3.27 (s, 3H, OCH_3), 3.75 (s, 3H, CO_2CH_3), 4.48 (dt, 1H, *J* = 7.8, 0.6 Hz, CH_2=CHC*H*O), 5.31 – 5.33 (m, 1H,

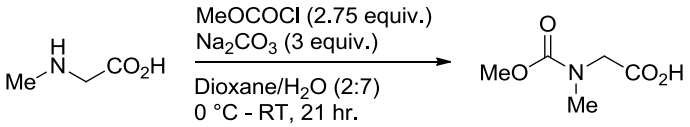
CH_2=CHCHO), 5.33 – 5.36 (m, 1H, CH_2=CHCHO), 5.99 (ddd, 1H, *J* = 17.1, 10.3, 7.8 Hz, CH_2=C*H*CHO), 7.70 – 7.71 (m, 2H, Ar-*H* Phth), 7.78 – 7.80 (m, 2H, Ar-*H* Phth); *anti* δ: 1.79 (s, 3H, NC(CH_3)CO_2), 3.32 (s, 3H, OCH_3), 3.77 (s, 3H, CO_2CH_3), 4.60 (dt, 1H, *J* = 8.62, 0.84 Hz, CH_2=CHC*H*O), 5.26 – 5.30 (m, 2H, CH_2=CHCHO), 5.73 (ddd, 1H, *J* = 17.1, 10.3, 7.7 Hz, CH_2=C*H*CHO), 7.70 – 7.71 (m, 2H, Ar-*H* Phth), 7.78 – 7.80 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 19.5, 52.4, 57.2, 65.5, 83.7, 120.5, 123.2, 131.7, 133.5, 134.0, 168.2, 170.6; *anti* δ: 19.3, 52.5, 56.8, 65.2, 83.1, 121.1, 123.4, 131.9, 133.0, 134.2, 168.3, 169.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{17}NO_5Na$ 326.1004, found 326.0997 $(M+Na)^+$.

(*Z*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)penta-2,4-dienoate (284)



FTIR (film/cm^{-1}) υ_{max}: 3025.4, 3003.7, 2985.9, 1704.2, 1689.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.71 (s, 3H, CO_2CH_3), 5.14 – 5.27 (m, 2H, H_2C=CHCH=C), 6.35 (dt, 1H, *J* = 16.8, 10.5 Hz, H_2C=C*H*CH=C), 7.61 (d, 1H, *J* = 10.5 Hz, H_2C=CHC*H*=C), 7.78 – 7.80 (m, 2H, Ar-*H* Phth), 7.91 – 7.93 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.7, 124.0, 129.1, 132.0, 133.8, 134.3, 134.4, 142.2, 163.4, 167.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{14}H_{11}NO_4Na$ 280.0586, found 280.0581 $(M+Na)^+$.

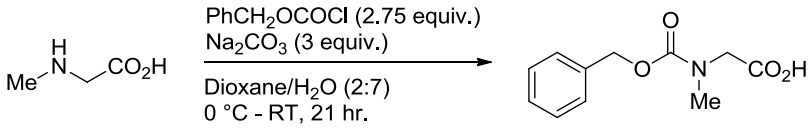
2-(Methoxycarbonyl(methyl)amino)acetic acid (295)



To a stirred solution of sarcosine **294** (3.49 g, 39.1 mmol, 1 equiv.) in water (140 mL) at 0 °C was added sodium carbonate (12.5 g, 117 mmol, 3 equiv.). To this solution was added a solution of methyl chloroformate (8.3 mL, 107 mmol, 2.75 equiv.) in dioxane (40 mL) *via* a dropping funnel over 5 minutes. The reaction was stirred for a further 30 minutes at 0 °C before warming to room temperature and stirring for a further 20 hours. The slurry was washed with ether (2 × 50 mL) and the aqueous acidified with 10% HCl to pH 1-2 and extracted with EtOAc (4 × 50 mL). Organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (4.20 g, 73%, 1.2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3019.8, 2956.0, 1701.2, 1666.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.92 & 2.93 (2s, 3H, CH_3OCON), 3.65 & 3.68 (2s, 3H, CH_3N), 3.96 & 4.02 (2s, 2H, NCH_2CO_2H), 11.37 (s, 1H, CO_2H); ^{13}C

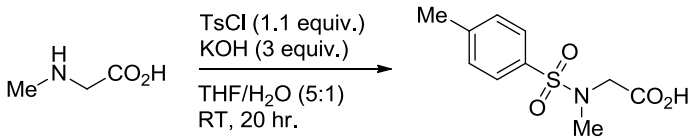
NMR (125 MHz, $CDCl_3$) δ: 35.2, 35.9, 50.1, 50.4, 53.2 (×2), 157.0, 157.7, 173.6, 173.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_5H_9NO_4Na$ 170.0429, found 170.0416 $(M+Na)^+$.

2-((Benzyloxycarbonyl)(methyl)amino)acetic acid (296)



To a stirred solution of sarcosine **294** (4.00 g, 44.9 mmol, 1 equiv.) in water (140 mL) at 0 °C was added sodium carbonate (14.3 g, 134 mmol, 3 equiv.). To this solution was added a solution of benzyl chloroformate (7 mL, 123 mmol, 2.75 equiv.) in dioxane (40 mL) *via* a dropping funnel over 5 minutes. The reaction was stirred for a further 30 minutes at 0 °C before warming to room temperature and stirring for a further 20 hours. The slurry was washed with ether (2 × 50 mL) and the aqueous acidified with 10% HCl to pH 1-2 and extracted with EtOAc (4 × 50 mL). Organic fractions were combined, dried over MgSO4, filtered and concentrated *in vacuo* to afford the crude acid as an oil. Upon storage at -18 °C solidification occurred to afford the title compound as an off-white solid (8.96 g, 90%, 1.3:1 rotamers). MP: 58 – 59 °C; lit. 58 - 59 °C;[167] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.03 (s, 3H, C*H*$_3$NCH$_2$), 4.06 & 4.11 (2s, 2H, NC*H*$_2$CO$_2$H), 5.15 & 5.18 (2s, 2H, PhC*H*$_2$OCON), 7.29 – 7.39 (m, 5H, Ar-*H* Ph), 11.37 (s, 1H, CO$_2$*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.4, 36.0, 50.2, 50.6, 67.6, 67.7, 127.9, 128.1, 128.5, 128.6, 136.3, 156.1, 157.0, 174.6, 174.8. All analytical data is in accordance with reported literature values.[168]

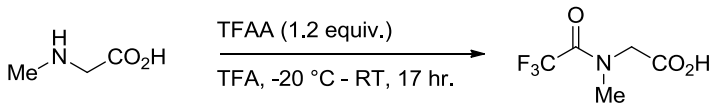
2-(*N*,4-Dimethylphenylsulfonamido)acetic acid (297)



To a stirred solution of sarcosine **294** (5.00 g, 56.1 mmol, 1 equiv.) in water (50 mL) was added potassium hydroxide (9.4 g, 168.4 mmol, 3 equiv.). To this was added a solution of *p*-toluenesulfonyl chloride (11.7 g, 61.7 mmol, 1.1 equiv.) in THF (250 mL) *via* a dropping funnel over 10 minutes. The reaction was stirred at room temperature for 20 hours, before acidifying with 10% HCl to pH 1-2 and extracting with EtOAc (5 × 100 mL), drying over $MgSO_4$, filtering and concentrating *in vacuo*. Purification was

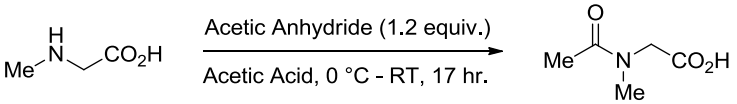
achieved by recrystalisation from acetone/hexane to afford the title compound as colourless solid (12.2 g, 90%). MP: 152 – 153 °C, Lit: 147 – 150 °C; FTIR (film/cm^{-1}) υ_{max}: 3070.5, 2958.3, 2932.6, 2895.8, 2858.0, 1728.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.45 (s, 3H, C*H*$_3$C$_6$H$_4$SO$_2$N), 2.89 (s, 3H, NC*H*$_3$), 4.00 (s, 2H, NC*H*$_2$CO$_2$H), 7.31 – 7.34 (m, 2H, Ar-*H* Ts), 7.70 – 7.72 (m, 2H, Ar-*H* Ts); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.5, 35.8, 50.7, 127.4, 129.7, 135.0, 143.9, 173.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_{10}H_{13}NO_4SNa$ 266.0463, found 266.0461 $(M+Na)^+$. All analytical data is in accordance with reported literature values.[169]

2-(2,2,2-Trifluoro-*N*-methylacetamido)acetic acid (298)



To a cooled solution of sarcosine **294** (2.22 g, 25.0 mmol, 1 equiv.) in dry trifluoroacetic acid (15 mL) at -10 °C, was added trifluoroacetic anhydride (4.4 mL, 30.0 mmol, 1.2 equiv.) over 30 minutes *via* syringe pump. After addition, the mixture was cooled to -20 °C and stirred for 16 hours, then at room temperature for 1 hour. Excess reagents and solvent were removed *in vacuo* before azeotroping with toluene (200 mL) to afford the title compound as a yellow solid (4.96 g, 100%, 2.9:1 rotamers). MP: 53 – 54 °C, Lit: 54.5 - 55.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.14 & 3.26 (2s, 3H, NC*H*$_3$), 4.24 & 4.27 (2s, 2H, NC*H*$_2$CO$_2$H), 9.12 (br, 1H, NCH$_2$CO$_2$*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 36.4, 36.5, 50.4, 115.0, 117.3, 158.0 (q, *J* = 37.6 Hz), 159.9 (q, *J* = 37.6 Hz), 172.8, 172.9; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{17}F_3NO_3Na$ 208.0197, found 208.0175 $(M+Na)^+$. All analytical data is in accordance with reported literature values.[170]

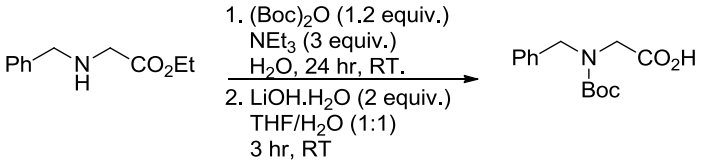
2-(*N*-methylacetamido)acetic acid (299)



To a cooled solution of sarcosine **294** (5.0 g, 56.1 mmol, 1 equiv.) in dry acetic acid (60 mL) at 0 °C, was added acetic anhydride (6.35 mL, 67.1 mmol, 1.2 equiv.) over 30 minutes *via* syringe pump. After addition, the mixture was stirred at 0 °C for 16 hours, then at room temperature for 1 hour. Excess reagents and solvent were removed *in vacuo* before azetroping with toluene (200 mL) to afford the title compound as a white

solid (6.15 g, 84%, 2.2:1 rotamers). MP: 138 – 140 °C, Lit: 134 - 134.5 °C;[171] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.06 & 2.15 (2s, 3H, C*H*$_3$CON), 2.96 & 3.13 (2s, 3H, $CH_3CON(CH_3)$), 4.11 & 4.19 (2s, 2H, NC*H*$_2$CO$_2$H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.7, 19.8, 33.7, 36.3, 48.7, 51.6, 170.9, 171.2, 172.7, 172.8. All analytical data is in accordance with reported literature values.[172]

2-(Benzyl(*tert*-butoxycarbonyl)amino)acetic acid (301)

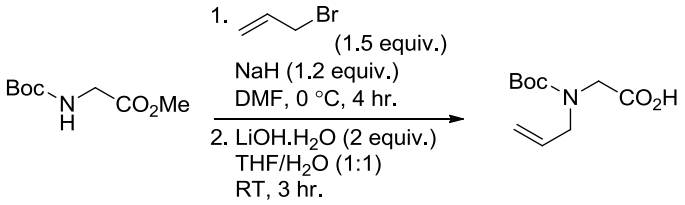


To a solution of *N*-benzyl glycine ethyl ester **300** (6.24 g, 32.3 mmol, 1 equiv.) in water (200 mL) was added triethylamine (13.5 mL, 96.9 mmol, 3 equiv.) and di-*tert*-butyl dicarbonate (8.45 g, 38.7 mmol, 1.2 equiv.) and stirred at room temperature for 24 hours. The reaction was quenched with aqueous HCl (10%, 100 mL) and extracted with EtOAc (5 × 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the ethyl 2-benzyl(*tert*-butoxycarbonyl)amino)acetate as a yellow oil (7.73 g, 82%, 1.3:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 2979.5, 1749.0, 1697.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, 3H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.48 (s, 9H, $(CH_3)_3COCON$), 3.78 & 3.93 (2s, 2H, PhC*H*$_2$N), 4.17 (q, 2H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.53 & 4.57 (2s, 2H, NC*H*$_2$CO$_2$), 7.21 – 7.37 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 28.3, 48.1, 51.5, 61.0, 80.7, 127.4, 127.6, 128.2, 128.6, 137.6, 155.8, 170.0; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{24}NO_4Na$ 294.1705, found 294.1693 $(M+Na)^+$.

To a solution of ethyl 2-benzyl(*tert*-butoxycarbonyl)amino)acetate (7.73 g, 26.3 mmol, 1 equiv.) in THF/water (200 mL, 1:1) was added lithium hydroxide (2.20 g, 52.7 mmol, 2 equiv.) and was stirred at room temperature for 3 hours. Acetic acid was added until pH 4 was reached then the solution was extracted with EtOAc (4 × 100 mL). The organics were dried over $MgSO_4$, filtered, concentrated *in vacuo* to afford a yellow solid. Toluene (200 mL) was added to azeotrope excess acetic acid. Purification was achieved by recrystallisation from cyclohexane to afford the title compound as a yellow solid (7.08 g, 100%, 1.3:1 rotamers). MP: 134 – 135 °C, Lit. 107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.48 (s, 9H, $(CH_3)_3COCON$), 3.82 & 3.93 (2s, 2H, NC*H*$_2$CO$_2$H), 4.51 & 4.55 (2s, 2H, PhC*H*$_2$N), 7.16 – 7.35 (m, 5H, Ar-*H* Ph), 8.34 (br, 1H, CO$_2$*H*); ^{13}C

NMR (125 MHz, $CDCl_3$) δ: 28.3, 28.4, 47.8, 48.1, 50.8, 51.6, 80.8, 81.1, 125.3, 127.5, 128.1, 128.2, 128.6, 129.0, 137.2, 137.3, 155.7, 156.3, 175.2, 175.5. All analytical data is in accordance with reported literature values.[173]

2-(Allyl(*tert*-butoxycarbonyl)amino)acetic acid (303)

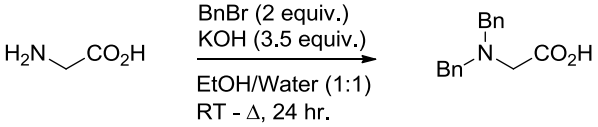


To a solution of *N*-(*tert*-butoxycarbonyl)glycine methyl ester **302** (2.00 g, 10.6 mmol, 1 equiv.) in DMF (100 mL) at 0 °C was added allyl bromide (1.34 mL, 15.9 mmol, 1.5 equiv.). Dried sodium hydride (0.30 g, 12.7 mmol. 1.2 equiv.) was added portionwise and the reaction stirred for 4 hours. The reaction was quenched with saturated NH_4Cl (100 mL) and extracted with EtOAc (4 × 50 mL), washed with saturated LiCl solution (2 × 50 mL) and brine (2 × 50 mL), dried over MgSO4, filtered and concentrated *in vacuo* to afford methyl 2-(allyl(*tert*-butoxycarbonyl)amino)acetate as a yellow oil (1.55 g, 64%, 1:1 rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 & 1.48 (2s, 9H, $(CH_3)_3COCON$), 3.73 & 3.75 (2s, 3H, CO_2CH_3), 3.86 & 3.89 (2d, 2H, J = 5.6 Hz, NCH_2CO_2), 3.94 – 3.98 (m, 2H, $NCH_2CH{=}CH_2$), 5.10 – 5.19 (m, 2H, $NCH_2CH{=}CH_2$), 5.72 - 5.85 (m, 1H, NCH2C*H*=CH_2);^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.5, 47.7, 48.1, 50.5, 51.0, 52.1, 80.6, 117.0, 117.8, 133.8, 133.9, 155.3, 155.8, 170.8. All analytical data is in accordance with reported literature values.[174]

To a solution of 2-(allyl(*tert*-butoxycarbonyl)amino)acetate (0.93 g, 4.00 mmol, 1 equiv.) in THF/water (20 mL, 1:1) was added lithium hydroxide (0.34 g, 8.00 mmol, 2 equiv.) and was stirred at room temperature for 3 hours. Acetic acid was added until pH 4 was reached then the solution was extracted with ethyl acetate (4 × 100 mL). The organics were dried over $MgSO_4$, filtered, concentrated *in vacuo* to afford a yellow solid. Toluene (200 mL) was added to azeotrope excess acetic acid to afford the title compound as a yellow solid (0.86 g, 100%, 1:1 rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.44 & 1.46 (2s, 9H, $(CH_3)_3COCON$), 3.89 (s, 2H, NCH_2CO_2), 3.95 – 3.99 (m, 2H, $NCH_2CH{=}CH_2$), 5.14 – 5.18 (m, 2H, $NCH_2CH{=}CH_2$), 5.74 – 5.83 (m, 1H, $NCH_2CH{=}CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.1, 47.6, 50.2, 50.8, 80.8, 117.1,

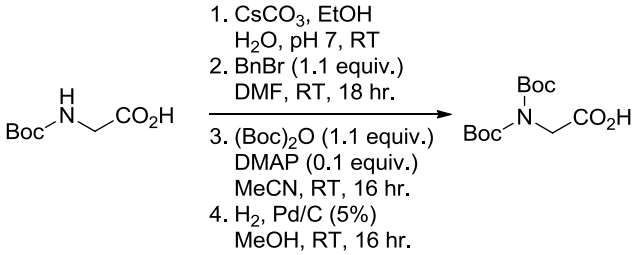
117.8, 133.2, 133.4, 155.2, 155.8, 175.2, 175.5. All analytical data is in accordance with reported literature values.[175]

2-(Dibenzylamino)acetic acid (304)



To a stirred solution of glycine **50** (1.29 g, 17.1 mmol, 1 equiv.) in water and ethanol (20 mL, 1:1) was added potassium hydroxide (3.46 g, 60.1 mmol, 3.5 equiv) followed by benzyl bromide (4.08 mL, 34.2 mmol, 2 equiv.) dropwise. The reaction was stirred at room temperature for 24 hours, then refluxed for 30 minutes. The mixture is cooled and ethanol removed *in vacuo* before acidifying with acetic acid to pH 6. The white solid was collected by filtration. Purification was achieved by recrystalisation from water to afford a white powder (2.33 g, 100%). MP: 198 – 200 °C, Lit: 192 – 194 °C;[176] ^{1}H NMR (500 MHz, d_6-DMSO) δ: 3.16 (s, 2H, NC*H*$_2$CO$_2$H), 3.75 (s, 4H, PhC*H*$_2$N), 7.24 – 7.37 (m, 10H, Ar-*H* Ph), 12.32 (br, 1H, CO$_2$*H*); ^{13}C NMR (125 MHz, d_6-DMSO) δ: 53.4, 57.3, 127.5, 128.7, 129.0, 139.5, 172.7. All analytical data is in accordance with reported literature values.[137]

Di-(*tert*-butoxycarbonyl)aminoacetic acid (305)



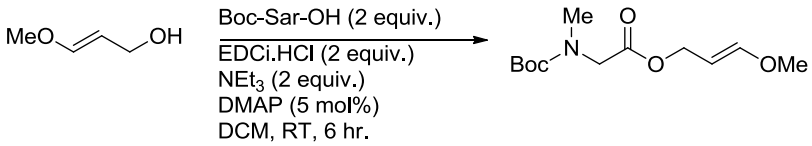
To a stirred solution of *N*-Boc-Gly-OH **184** (0.88 g, 5 mmol, 1 equiv.) in ethanol and water (25 mL, 7:3) was added a 1M $CsCO_3$ solution dropwise until pH 7 was reached. The solvents were removed *in vacuo* and the white salt dried under vacuum. The cesium salt was taken up in DMF (25 mL), treated with benzyl bromide (0.65 mL, 5.5 mmol, 1.1 equiv.) and stirred for 18 hours at room temperature. Solvent was removed *in vacuo* and the residue taken up in water (100 mL) and extracted with EtOAc (3 × 75 mL). Organics were washed with water (2 × 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford benzyl 2-(*tert*-butoxycarbonylamino)acetate as a cream solid (1.32 g, 100%). MP: 73 – 77 °C, Lit: 72 – 73 °C;[177] ^{1}H NMR (500 MHz, $CDCl_3$)

δ: 1.46 (s, 9H, (C*H*$_3$)$_3$COCON), 3.97 (d, 2H, *J* = 5.8 Hz, NC*H*$_2$CO$_2$), 5.04 (br, 1H, (CH$_3$)$_3$COCON*H*), 5.20 (s, 2H, PhC*H*$_2$O$_2$C), 7.33 – 7.40 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 28.3, 42.5, 67.1, 80.1, 128.4, 128.5, 128.6, 135.3, 155.7, 170.3. All analytical data is in accordance with reported literature values.[178]

To a solution of benzyl 2-(*tert*-butoxycarbonylamino)acetate (1.27 g, 4.8 mmol, 1 equiv.) and DMAP (0.06 g, 0.5 mmol, 0.1 equiv.) in acetonitrile was added a solution of di-*tert*-butyl dicarbonate (1.15 g, 5.3 mmol, 1.1 equiv.) in acetonitrile (2.6 mL). The solution was stirred at room temperature 16 hours before concentrating *in vacuo*. The residue was taken up in EtOAc (50 mL) and washed with brine (2 × 50 mL), dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* to afford benzyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate as a yellow oil (1.35 g, 78%). FTIR (film/cm^{-1}) υ_{max}: 3034.6, 2981.3, 2934.9, 1797.0, 1759.5, 1698.1; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.48 (s, 18H, (C*H*$_3$)$_3$COCON), 4.39 (s, 2H, NC*H*$_2$CO$_2$), 5.20 (s, 2H, CO$_2$C*H*$_2$Ph), 7.31 - 7.40 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 28.0, 47.4, 66.9, 83.1, 128.3, 128.4, 128.5, 151.9, 169.1; HRMS (ESI, +ve) *m/z*: calcd. for C$_{19}$H$_{27}$NO$_6$Na 388.1736, found 388.1716 (M+Na)$^+$. All analytical data is in accordance with reported literature values.[138]

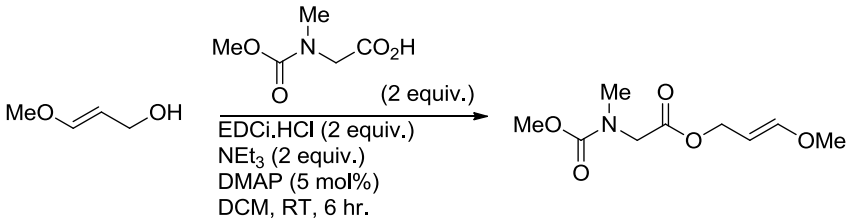
To a solution of benzyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (1.35 g, 3.7 mmol, 1 equiv.) in methanol (20 mL) was added catalytic palladium/carbon under an atmosphere of hydrogen and stirred at room temperature for 16 hours. Filtration through celite and concentrating *in vacuo* affords a cream solid. This solid was taken up in ether (100 mL) and washed with saturated sodium bicarbonate solution (3 × 50 mL). The aqueous was acidified with 1M HCl solution to pH 1, and extracted with ether, dried over MgSO$_4$, filtered and concentrated *in vacuo* to afford the title compound as a colourless crystalline product (1.01 g, 100%). MP: 115 – 117 °C; Lit: 113.5 – 114 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.47 (s, 18H, (C*H*$_3$)$_3$COCON), 4.36 (s, 2H, NC*H*$_2$CO$_2$), 11.18 (br, 1H, CO$_2$*H*); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 27.9, 47.0, 83.4, 151.7, 175.2; HRMS (ESI, +ve) *m/z*: calcd. for C$_{12}$H$_{21}$NO$_6$Na 298.1267, found 298.1260. All analytical data is in accordance with reported literature values.[138]

(*E*)-3-Methoxyallyl 2-(*tert*-butoxycarbonyl(methyl)amino)acetate (306)



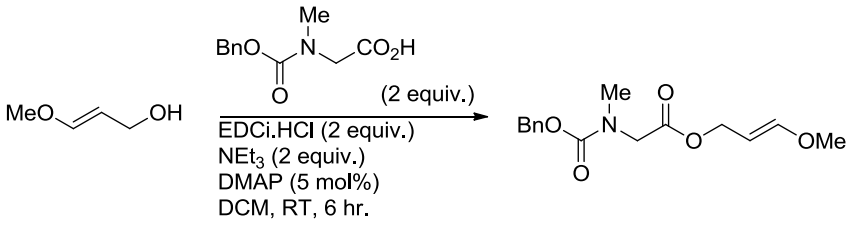
EDCi.HCl (3.81 g, 19.9 mmol), triethylamine (2.75 mL, 19.9 mmol), Boc-Sar-OH **294** (3.76 g, 19.9 mmol), catalytic DMAP and (*E*)-3-(methoxy)prop-2-enol **224** (0.88 g, 9.94 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (3.79 g, 77%, 1.1:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3006.0, 2976.4, 2933.5, 2841.2, 1746.0, 1695.0, 1653.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42 & 1.47 (2s, 9H, $(CH_3)_3COCON$), 2.91 & 2.93 (2s, 3H, $N(CH_3)CH_2CO_2$), 3.57 (s, 3H, $OCH_2CH{=}CHOCH_3$), 3.87 & 3.96 (2s, 3H, NCH_2CO_2), 4.57 (app. dd, 2H, *J* = 7.9, 2.9 Hz, $OCH_2CH{=}CHO$), 4.88 – 4.96 (m, 1H, $OCH_2CH{=}CHO$), 6.64 (app. t, 1H, *J* = 11.3 Hz, $OCH_2CH{=}CHO$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.2, 28.4, 35.5, 35.6, 50.4, 51.2, 56.1, 63.2, 80.1, 96.6, 153.5, 153.7, 155.5, 156.1, 169.9 (×2); HRMS (ESI, +ve) *m/z*: calcd. for $C_{12}H_{21}NNaO_5$ 282.1317, found 282.1320 $(M+Na)^+$.

(*E*)-3-Methoxyallyl 2-(methoxycarbonyl(methyl)amino)acetate (307)



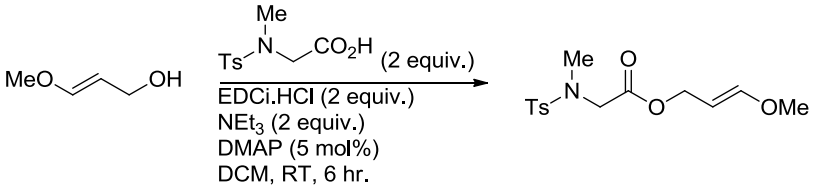
EDCi.HCl (1.48 g, 7.74 mmol), triethylamine (1.1 mL, 7.74 mmol), 2-(methoxycarbonyl(methyl)amino)acetic acid **295** (1.14 g, 7.74 mmol), catalytic DMAP and 3-methoxyprop-2-en-1-ol **224** (0.34 g, 3.89 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (0.73 g, 87%, 1.2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 2958.4, 2839.0, 1744.2, 1701.0, 1654.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.96 & 2.99 (2s, 3H, NCH_3), 3.58 (s, 3H, $OCH_2CH{=}CHOCH_3$), 3.69 & 3.74 (2s, 3H, CH_3OCON), 3.95 & 4.02 (2s, 2H, NCH_2CO_2), 4.58 (d, 2H, *J* = 7.6 Hz, $OCH_2CH{=}CHOCH_3$), 4.93 (dt, 1H, *J* = 12.5, 7.6 Hz, $OCH_2CH{=}CHOCH_3$), 6.65 (d, 1H, *J* = 12.5 Hz, $OCH_2CH{=}CHOCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.2, 35.9, 50.5, 50.7, 52.9 (×2), 61.1 (×2), 63.3, 96.5 (×2), 153.6, 153.7, 156.7, 157.3, 169.5, 169.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_9H_{15}NO_5Na$ 240.0848, found 240.0824 $(M+Na)^+$.

(*E*)-3-Methoxyallyl 2-(((benzyloxy)carbonyl)(methyl)amino)acetate (308)



EDCi.HCl (1.41 g, 7.35 mmol), triethylamine (1.0 mL, 7.35 mmol), 2-((benzyloxycarbonyl)(methyl)amino)acetic acid **296** (1.604 g, 7.35 mmol), catalytic DMAP and 3-methoxyprop-2-en-1-ol **224** (0.32 g, 3.68 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (1.05 g, 97%, 1.2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3015.2, 2985.9, 2843.7, 1734.2, 1695.0, 1659.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.01 & 3.02 (2s, 3H, NC*H*$_3$), 3.55 & 3.58 (2s, 3H, OCH$_2$CH=CHOC*H*$_3$), 3.99 & 4.05 (2s, 2H, NC*H*$_2$CO$_2$), 4.54 & 4.59 (2d, 2H, *J* = 7.9 Hz, OC*H*$_2$CH=CHOCH$_3$), 4.87 & 4.92 (2dt, 1H, *J* = 12.6, 7.9 Hz, OCH$_2$C*H*=CHOCH$_3$), 5.14 & 5.17 (2s, 2H, PhC*H*$_2$O), 6.64 (app. t, 1H, *J* = 12.6 Hz, OCH$_2$CH=C*H*OCH$_3$), 7.29 – 7.39 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.3, 36.1, 50.7, 50.8, 56.1, 63.4 (×2), 67.4 (×2), 67.5, 96.4, 96.5, 127.7, 127.8, 128.0 (×2), 128.4, 128.5, 136.6 (×2), 153.7 (×2), 156.1, 156.7, 169.5, 169.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_{15}H_{19}NO_5Na$ 316.1161, found 316.1185 $(M+Na)^+$.

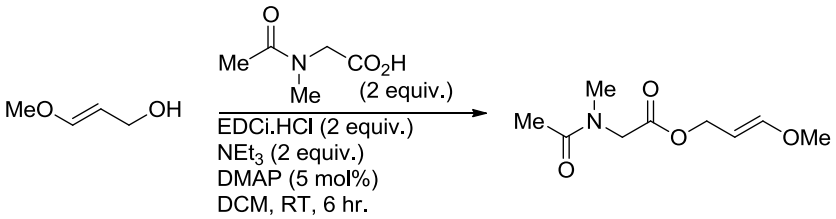
(*E*)-3-Methoxyallyl 2-(*N*,4-dimethylphenylsulfonamido)acetate (309)



EDCi.HCl (1.61 g, 8.40 mmol), triethylamine (1.2 mL, 8.40 mmol), 2-(*N*,4-dimethylphenylsulfonamido)acetic acid **297** (2.07 g, 8.40 mmol), catalytic DMAP and (*E*)-3-(methoxy)prop-2-enol **224** (0.38 g, 4.20 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (0.80 g, 60%). FTIR (film/cm^{-1}) υ_{max}: 2963.7, 2938.1, 2891.0, 2837.7, 1747.1, 1654.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.42 (s, 3H, C*H*$_3$C$_6$H$_4$SO$_2$), 2.86 (s, 3H, NC*H*$_3$), 3.55 (2, 3H, OCH$_2$CH=CHOC*H*$_3$), 3.94, (s, 2H, NC*H*$_2$CO$_2$), 4.48 (d, 2H, *J* = 8.1 Hz, OC*H*$_2$CH=CHO), 4.84 (dt, 1H, *J* = 12.5, 8.1 Hz, OCH$_2$C*H*=CHO), 6.56 (d, 1H, *J* = 12.5 Hz, OCH$_2$CH=C*H*O), 7.30 (m, 2H, Ar-*H* Ph), 7.69 (m, 2H, Ar-*H* Ph); ^{13}C NMR (125

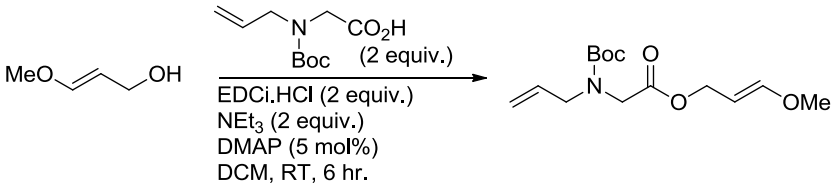
MHz, $CDCl_3$) δ: 21.5, 35.7, 51.1, 56.2, 63.5, 96.3, 127.5, 129.6, 135.2, 143.5, 153.8, 168.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{14}H_{19}NO_5SNa$ 336.0882, found 336.0873 $(M+Na)^+$.

(*E*)-3-Methoxyallyl 2-(*N*-methylacetamido)acetate (310)



EDCi.HCl (0.76 g, 3.96 mmol), triethylamine (0.55 mL, 3.96 mmol), 2-(*N*-methylacetamido)acetic acid **299** (0.52 g, 3.96 mmol), catalytic DMAP and (*E*)-3-(methoxy)prop-2-enol **224** (0.18 g, 1.98 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (0.23 g, 73%, 2.5:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3006.0, 2977.0, 2933.5, 2879.8, 1703.6, 1695.1, 1669.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.05 & 2.15 (2s, 3H, C*H*$_3$CON), 2.97 & 3.08 (2s, 3H, NC*H*$_3$), 3.58 & 3.59 (2s, 3H, OCH$_2$CH=CHOC*H*$_3$), 4.01 & 4.12 (2s, 2H, NC*H*$_2$CO$_2$), 4.57 & 4.61 (2d, 2H, *J* = 8.0 Hz, OC*H*$_2$CH=CHOCH$_3$), 4.89 – 4.96 (m, 1H, OCH$_2$C*H*=CHOCH$_3$), 6.62 – 6.68 (m, 1H, OCH$_2$CH=C*H*OCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.3, 21.4, 34.7, 37.2, 49.2, 52.6, 56.1, 56.2, 63.4, 63.8, 96.2, 96.6, 153.6, 154.2, 168.9, 169.3, 171.0, 171.3; HRMS (ESI, +ve) *m/z*: calcd. for $C_9H_{16}NO_4Na$ 202.1079, found 202.1057 $(M+H)^+$.

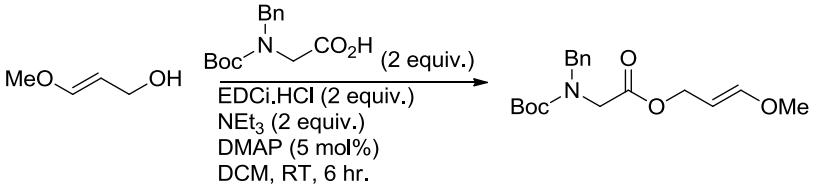
(*E*)-3-Methoxyallyl 2-(allyl(*tert*-butoxycarbonyl)amino)acetate (311)



EDCi.HCl (0.60 g, 3.15 mmol), triethylamine (0.45 mL, 3.15 mmol), 2-(allyl(*tert*-butoxycarbonyl)amino)acetic acid **303** (0.52 g, 3.96 mmol), catalytic DMAP and (*E*)-3-(methoxy)prop-2-enol **224** (0.18 g, 1.98 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (0.34 g, 60%, 1:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3006.1, 2963.9, 2945.4, 1739.7, 1698.9, 1650.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.44 & 1.47 (2s, 9H, (C*H*$_3$)$_3$COCON), 3.58 (s, 3H, OCH$_2$CH=CHOC*H*$_3$), 3.82 – 3.97 (m, 4H, NC*H*$_2$CO$_2$ & NC*H*$_2$CH=CH$_2$), 4.56 (d, 2H, *J*

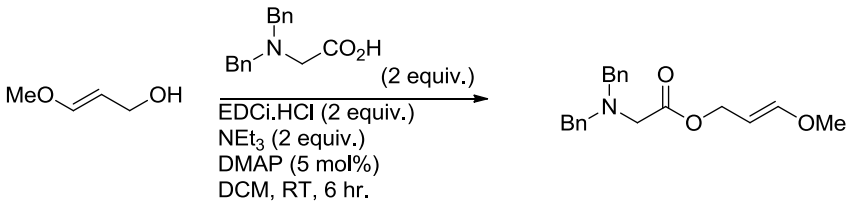
= 7.6 Hz, OCH_2CH=CHOCH$_3$), 4.89 – 4.96 (m, 1H, OCH$_2$CH=CHOCH$_3$), 5.11 – 5.19 (m, 2H, NCH$_2$CH=CH_2), 5.75 – 5.84 (m, 1H, NCH$_2$CH=CH$_2$), 6.65 (app. t, 1H, J = 11.6 Hz, OCH$_2$CH=CHOCH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 28.2, 28.3, 47.8, 48.2, 50.3, 50.7, 56.1(×2), 63.1, 63.2, 80.3 (×2), 96.7, 96.9, 116.8, 117.6, 133.7, 133.8, 153.5, 153.7, 155.2, 155.6, 170.0, 170.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{14}H_{23}NO_5Na$ 308.1474, found 308.1485 $(M+Na)^+$.

(*E*)-3-Methoxyallyl 2-(benzyl(*tert*-butoxycarbonyl)amino)acetate (312)



EDCi.HCl (0.92 g, 4.81 mmol), triethylamine (0.66 mL, 4.81 mmol), 2-(benzyl(*tert*-butoxycarbonyl)amino)acetic acid (1.28 g, 4.81 mmol), catalytic DMAP and (*E*)-3-(methoxy)prop-2-enol **224** (0.21 g, 2.41 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil. (0.69 g, 85%, 1.2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 2976.8, 2939.3, 2836.4, 1745.2, 1697.0, 1654.0; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.47 & 1.48 (2s, 9H, (CH_3)$_3$COCON), 3.57 (s, 3H, OCH$_2$CH=CHOCH_3), 3.77 & 3.92 (2s, 2H, NCH_2CO$_2$), 4.50 – 4.56 (m, 4H, OCH_2CH=CHOCH$_3$ & PhCH_2N), 4.86 – 4.92 (m, 1H, OCH$_2$CH=CHOCH$_3$), 6.63 (dd, 1H, J = 12.9, 4.4 Hz, OCH$_2$CH=CHOCH$_3$), 7.21 – 7.35 (5H, m, Ar-H Ph); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 28.3 (×2), 47.8, 48.2, 51.0, 51.5, 56.1(×2), 63.2 (×2), 80.5, 80.7, 96.6 (×2), 127.4, 127.5 (×2), 128.1 (×2), 128.6 (×2), 137.3, 137.6, 153.5, 153.7, 155.6, 155.8, 169.9, 170.0; HRMS (ESI, +ve) *m/z*: calcd. for $C_{18}H_{25}NO_5Na$ 358.1630, found 358.1611 $(M+Na)^+$.

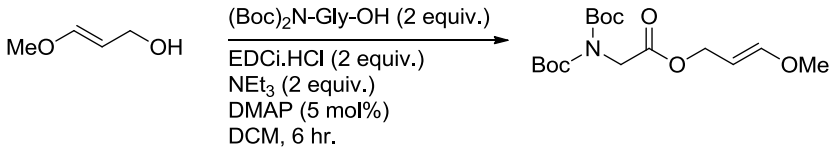
(*E*)-3-Methoxyallyl 2-(dibenzylamino)acetate (313)



EDCi.HCl (0.98 g, 5.12 mmol), triethylamine (0.72 mL, 5.12 mmol), 2-(dibenzylamino)acetic acid **304** (1.34 g, 5.12 mmol), catalytic DMAP and 3-methoxyprop-2-en-1-ol **224** (0.23 g, 2.60 mmol) were combined according to general

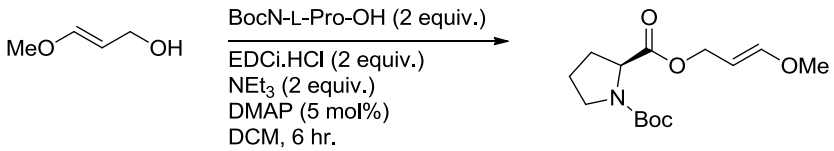
procedure 3, to afford the title compound as a cream oil (0.68 g, 76%). FTIR (film/cm^{-1}) υ_{max}: 3004.2, 3000.1, 2967.1, 1743.1, 1701.0, 1655.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.21 (s, 2H, NCH_2CO$_2$), 3.50 (s, 3H, OCH$_2$CH=CHOCH_3), 3.74 (s, 4H, PhCH_2N), 4.45 (d, 2H, *J* = 7.7 Hz, OCH_2CH=CHO), 4.84 (dt, 1H, *J* = 12.5, 7.7 Hz, OCH$_2$C*H*=CHO), 6.57 (d, 1H, *J* = 12.5 Hz, OCH$_2$CH=C*H*O), 7.14 – 7.34 (m, 10H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 54.0, 56.5, 58.1, 62.8, 97.4, 127.5, 128.7, 129.3, 139.4, 153.8, 171.8; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{27}NO_7Na$ 368.1685, found 368.1701 $(M+Na)^+$.

(*E*)-3-Methoxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (314)



EDCi.HCl (1.01 g, 5.27 mmol), triethylamine (0.74 mL, 5.27 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (1.15 g, 5.27 mmol), catalytic DMAP and (*E*)-3-methoxyprop-2-enol **224** (0.31 g, 2.63 mmol) were combined according to general procedure 3 to afford the title compound as a yellow oil (0.85 g, 70%). FTIR (film/cm^{-1}) υ_{max}: 2980.8, 2936.5, 1732.0, 1697.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.49 (s, 18H, (CH_3)$_3$COCON), 3.55 (s, 3H, OCH$_2$CH=CHOCH_3), 4.30 (s, 2H, NCH_2CO$_2$), 4.56 (d, 2H, *J* = 7.9 Hz, OCH_2CH=CHOCH$_3$), 4.91 (dt, 1H, *J* = 12.7, 7.9 Hz, OCH$_2$C*H*=CHOCH$_3$), 6.63 (d, 1H, *J* = 12.7 Hz, OCH$_2$CH=C*H*OCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0, 47.4, 56.1, 63.3, 83.0, 96.6, 151.9, 153.6, 169.2; HRMS (ESI, +ve) *m/z* calcd. for $C_{12}H_{21}NO_7Na$ 368.1685, found 368.1673 $(M+Na)^+$.

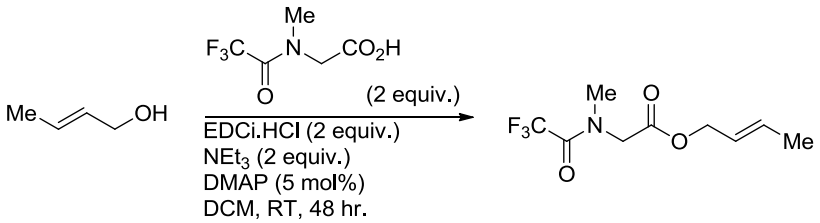
(*S*,*E*)-1-*tert*-Butyl 2-(3-methoxyallyl) pyrrolidine-1,2-dicarboxylate (315)



EDCi.HCl (1.52 g, 7.95 mmol), triethylamine (1.10 mL, 7.95 mmol), Boc-L-Pro-OH (1.71 g, 7.95 mmol), catalytic DMAP and (*E*)-3-methoxyprop-2-enol **224** (0.35 g, 3.97 mmol) were combined according to general procedure 3. Purifcation was achieved by flash chromatography (4:1 Pet/EtOAC + 2% NEt_3) to afford the title compound as a colourless oil (0.73 g, 65%).$[\alpha]_D^{20}$ -54° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 3072.0,

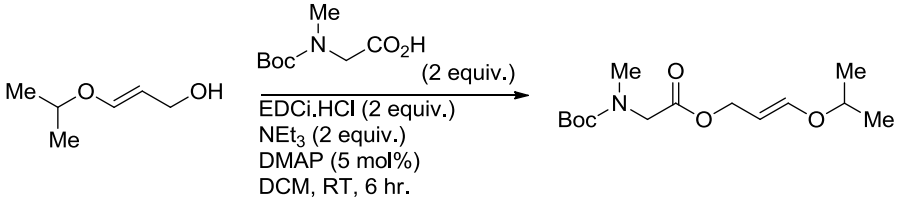
2976.1, 2882.9, 1744.7, 1698.3, 1656.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 & 1.40 (2s, 9H, $(CH_3)_3COCON$), 1.72 – 2.23 (m, 4H, CH_2CH_2CH), 3.23 – 3.55 (m, 2H, NCH_2), 3.50 & 3.51 (2s, 3H, OCH_3), 4.08 – 4.17 & 4.19 – 4.27 (2m, 1H, NC*H*), 4.44 – 4.55 (m, 2H, $OCH_2CH{=}CHO$), 4.78 – 4.92 (m, 1H, $OCH_2CH{=}CHO$), 6.56 & 6.58 (2d, 1H, *J* = 12.6 Hz, $OCH_2CH{=}CHO$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.4, 14.5, 24.0, 24.7, 28.7, 28.8, 30.2, 31.2, 46.7, 46.9, 59.3, 59.6, 60.8, 63.4, 77.0, 77.4, 77.6, 77.8, 80.0, 80.2, 154.0, 154.2, 173.3, 176.3; HRMS (ESI, +ve) *m/z* calcd. for $C_{14}H_{23}NO_5Na$ 308.1474, found 308.1463 $(M+Na)^+$.

(*E*)-But-2-enyl 2-(2,2,2-trifluoro-*N*-methylacetamido)acetate (316)



EDCi.HCl (0.21 g, 1.10 mmol), triethylamine (0.15 mL, 1.10 mmol), 2-(2,2,2-trifluoro-*N*-methylacetamido)acetic acid **298** (0.20 g, 1.10 mmol), catalytic DMAP and crotyl alcohol **226** (0.05 mL, 0.55 mmol) were combined according to general procedure 3, with a reaction time of 48 hours, to afford the title compound as a yellow oil. (0.08 g, 60%, 2.4:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3022.6, 2951.3, 1747.9, 1694.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.76 (d, 3H, *J* = 6.3 Hz, $OCH_2CH{=}CHCH_3$), 3.13 & 3.24 (2s, 3H, NCH_3), 4.19 (s, 2H, NCH_2CO_2), 4.63 (app. t, 2H, *J* = 6.7 Hz, $OCH_2CH{=}CHCH_3$), 5.57 – 5.65 (m, 1H, $OCH_2CH{=}CHCH_3$), 5.81 – 5.91 (m, 1H, $OCH_2CH{=}CHCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.8, 36.2, 50.5, 66.4, 66.6, 111.9, 112.0, 114.8, 114.9, 117.6, 117.7, 120.5, 120.6, 124.0, 124.2, 132.6, 132.9, 157.7 (q, *J* = 37.2 Hz), 167.3, 167.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_9H_{12}NO_3F_3Na$ 262.0667, found 262.0653 $(M+Na)^+$.

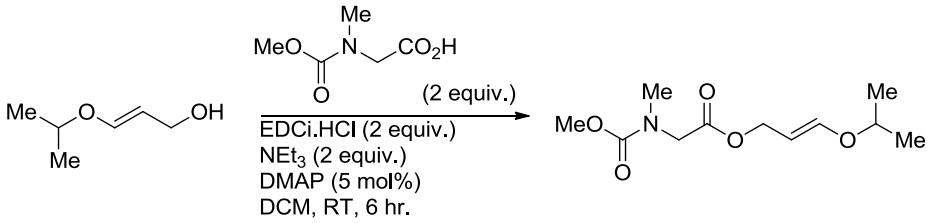
(*E*)-3-Isopropoxyallyl 2-((*tert*-butoxycarbonyl)(methyl)amino)acetate (320)



EDCi.HCl (0.68 g, 3.50 mmol), triethylamine (0.48 mL, 3.50 mmol), Boc-Sar-OH **294** (0.68 g, 3.5 mmol), catalytic DMAP and 3-isopropoxyprop-2-en-1-ol **248** (0.21 g, 1.75

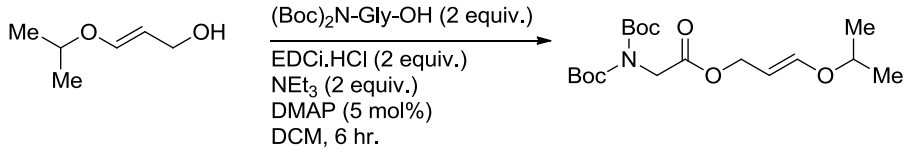
mmol) were combined according to general procedure 3 omitting the citric acid wash, to afford the title compound as a colourless oil (0.25 g, 49%, 1:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 2977.4, 2939.1, 2878.8, 1744.3, 1701.7, 1668.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.16 (d, 6H, *J* = 6.0 Hz, OCH(C*H*$_3$)$_2$), 1.35 & 1.40 (2s, 9H, (C*H*$_3$)$_3$COCON), 2.84 & 2.85 (2s, 3H, NC*H*$_3$), 3.79 & 3.88 (2s, 2H, NC*H*$_2$CO$_2$), 3.98 (sept, 1H, *J* = 6.0 Hz, OC*H*(CH$_3$)$_2$), 4.47 (d, 2H. *J* = 8.5 Hz, OC*H*$_2$CH=CHO), 4.86 – 4.97 (m, 1H, OCH$_2$C*H*=CHO), 6.40 (dd, 1H, *J* = 12.5, 6.3 Hz, OCH$_2$CH=C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.4, 28.4, 35.9, 52.2, 63.7, 73.6, 80.4, 99.1, 136.5, 152.2, 170.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{14}H_{25}NO_5Na$ 310.1630, found 360.1645 $(M+Na)^+$.

(*E*)-3-Isopropoxyallyl 2-(methoxycarbonyl(methyl)amino)acetate (321)



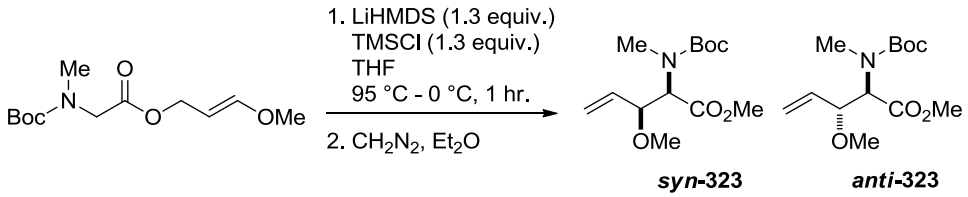
EDCi.HCl (1.20 g, 6.26 mmol), triethylamine (0.90 mL, 6.26 mmol), 2-(methoxycarbonyl(methyl)amino)acetic acid **295** (0.92 g, 6.26 mmol), catalytic DMAP and 3-isopropoxyprop-2-en-1-ol **248** (0.34 g, 3.12 mmol) were combined according to general procedure 3 omitting the citric acid wash, to afford the title compound as a yellow oil. (0.36 g, 47%, 1.1:1 rotamers) FTIR (film/cm^{-1}) υ_{max}: 2977.0, 2933.5, 2879.8, 1745.4, 1703.6, 1669.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (d, 6H, *J* = 6.1 Hz, OCH$_2$CH=CHOCH(C*H*$_3$)$_2$), 2.96 & 2.98 (2s, 3H, NC*H*$_3$), 3.69 & 3.73 (2s, 3H, C*H*$_3$OCON), 3.95 & 4.02 (2s, 2H NC*H*$_2$CO$_2$), 4.07 (quin, 1H, *J* = 6.1 Hz, OCH$_2$CH=CHOC*H*(CH$_3$)$_2$), 4.56 (d, 2H, *J* = 8.0 Hz, OC*H*$_2$CH=CHOCH(CH$_3$)$_2$), 5.01 (dt, 1H, *J* = 12.4, 8.0 Hz, OCH$_2$C*H*=CHOCH(CH$_3$)$_2$), 6.48 (dd, 1H, *J* = 12.4, 5.3 Hz, OCH$_2$CH=C*H*OCH(CH$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.0, 35.2, 35.9, 50.6, 50.8, 52.9, 53.0, 63.6, 73.4 (×2), 98.6, 151.8, 151.9, 157.4, 169.5, 169.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_{11}H_{19}NO_5Na$ 268.2620, found 268.2624 $(M+Na)^+$.

(*E*)-3-Isopropyloxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (322)



EDCi.HCl (0.79 g, 4.12 mmol), triethylamine (0.60 mL, 4.12 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (1.13 g, 4.12 mmol), catalytic DMAP and (*E*)-3-(isopropoxy)prop-2-enol **248** (0.24 g, 2.06 mmol) were combined according to general procedure 3 omitting the citric acid wash, to afford the title compound as a brown oil (0.72 g, 94%). FTIR (film/cm^{-1}) υ_{max}: 2978.5, 2936.4, 1757.1, 1736.3, 1697.0, 1671.0; ^{1}H NMR (500 MHz, CD_2Cl_2) δ: 1.21 (d, 6H, *J* = 6.3 Hz, $(CH_3)_2CHO$), 1.49 (s, 18H, $(CH_3)_3COCON$), 4.12 (sept, 1H, *J* = 6.3 Hz, $(CH_3)_2CHO$), 4.27 (s, 2H, NCH_2CO_2), 4.55 (d, 2H, *J* = 7.8 Hz, $OCH_2CH{=}CHO$), 4.97 (dt, 1H, *J* = 12.8, 7.8 Hz, $OCH_2CH{=}CHO$), 6.62 (d, 1H, *J* = 12.8 Hz, $OCH_2CH{=}CHO$); ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 21.4, 27.3, 47.1, 63.1, 72.9, 82.1, 98.6, 151.8, 152.0, 168.8; HRMS (ESI, +ve) *m/z*: calcd. for $C_{18}H_{31}NO_7Na$ 396.1998, found 396.2005 $(M+Na)^+$.

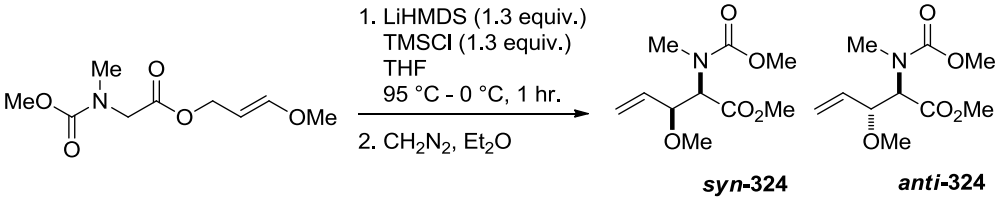
(±)-(2*R*,3*S*)-Methyl 2-((*tert*-butoxycarbonyl)(methyl)amino)-3-methoxypent-4-enoate (323)



(*E*)-3-Methoxyallyl 2-((*tert*-butoxycarbonyl)(methyl)amino)acetate **306** (0.13 g, 0.49 mmol), TMSCl (0.08 mL, 0.64 mmol) and LiHMDS (0.64 mL, 0.64 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (8:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.07 g, 73%, dr 2:1 obtained as a mixture of 2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3012.4, 2998.6, 1704.2, 1659.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-323**: 1.42 – 1.45 (m, 9H, $(CH_3)_3COCON$), 2.84 - 2.94 (m, 3H, NCH_3), 3.27 – 3.30 (m, 3H, OCH_3), 3.73 & 3.74 (2s, 3H, CO_2CH_3), 4.02 – 4.25 (m, 1H, $H_2C{=}CHCHOCH_3$), 4.31 - 5.04 (4 app. d, 1H, *J* = 5.4 Hz, $NCHCO_2$), 5.28 – 5.36 (m, 2H, $H_2C{=}CHCHOCH_3$), 5.68 (app. ddd, 1H, *J* = 6.9, 6.5, 3.5 Hz, $H_2C{=}CHCHOCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-323**: 28.3 (×2), 32.4, 32.8, 51.9, 52.0, 57.1, 57.4,

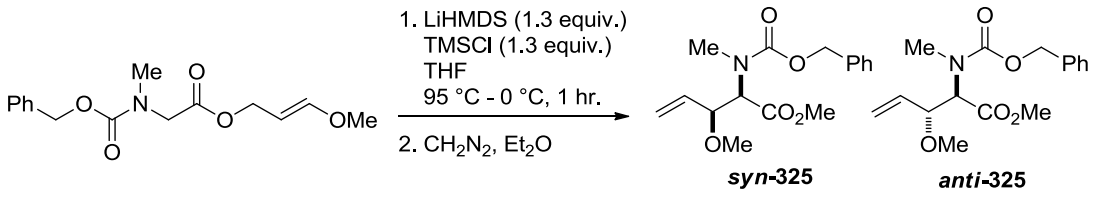
62.5, 62.7, 79.9, 80.2, 81.8, 82.0, 118.6, 119.1, 133.9, 134.4, 155.5, 156.6, 170.1, 170.3. HRMS (ESI, +ve) *m/z*: calcd. for $C_{13}H_{23}NO_5Na$ 296.1474, found 296.1493 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 3-methoxy-2-((methoxycarbonyl)(methyl)amino)pent-4-enoate (324)



(*E*)-3-Methoxyallyl 2-((methoxycarbonyl)(methyl)amino)acetate **307** (0.11 g, 0.52 mmol), TMSCl (0.09 mL, 0.68 mmol) and LiHMDS (0.68 mL, 0.68 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (8:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.05 g, 42% dr 1:1 obtained as a mixture of 2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 2998.2, 2997.7, 1708.2, 1657.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-324**: 2.88 & 2.99 (2s, 3H, NCH_3), 3.28 & 3.30 (2s, 3H, OCH_3), 3.66 – 3.76 (m, 6H, CO_2CH_3 & NCO_2CH_3), 4.01 – 4.28 (m, 1H, H_2C=CHC*H*O), 4.55 – 5.08 (app. d, 1H, *J* = 5.4 Hz, NC*H*CO_2), 5.32 – 5.39 (m, 2H, H_2C=CHCHO), 5.63 – 5.78 (m, 1H, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-324**: 32.4 (×2), 52.1, 53.0, 56.7, 57.5, 61.9, 62.1, 81.4, 81.5, 81.9 (×2), 119.0, 120.2, 133.7, 134.6, 156.5, 158.1, 170.1, 170.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{10}H_{17}NO_5Na$ 254.1004, found 254.0993 $(M+Na)^+$.

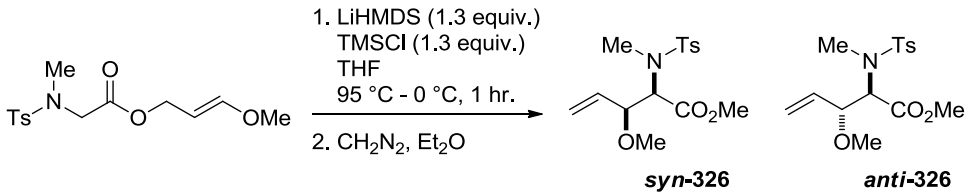
(±)-(2*R*,3*S*)-Methyl 2-(((benzyloxy)carbonyl)(methyl)amino)-3-methoxypent-4-enoate (325)



(*E*)-3-Methoxyallyl 2-((benzyloxycarbonyl)(methyl)amino)acetate **308** (0.12 g, 0.39 mmol), TMSCl (0.07 mL, 0.52 mmol) and LiHMDS (0.52 mL, 0.52 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (8:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.07 g, 41%, dr 2:1 obtained as a mixture of 2:1

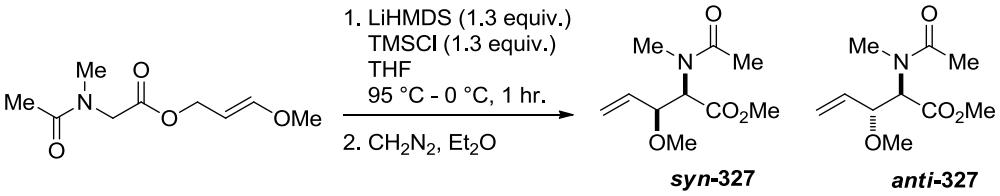
rotamers). FTIR (film/cm^{-1}) υ_{max}: 3014.2, 2988.7, 2985.3, 1704.5, 1698.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-325**: 2.91 & 2.93 (2s, 3H, NCH_3), 3.29 & 3.30 (2s, 3H, OCH_3), 3.70 & 3.76 (2s, 3H, CO_2CH_3), 4.00 – 4.29 (m, 1H, H_2C=CHC*H*O), 4.60 – 5.10 (4 app. d, 1H, *J* = 8.6 Hz, NC*H*CO_2), 5.11 – 5.19 (m, 2H, PhCH_2O), 5.27 – 5.38 (m, 2H, H_2C=CHCHO), 5.54 – 5.77 (m, 1H, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-325**: 32.6, 32.7, 52.1, 52.2, 56.7, 57.2, 61.6, 62.0, 67.4, 67.5, 81.5, 81.9, 119.0, 119.5, 120.3, 120.6, 127.7, 127.9, 133.7, 134.0, 136.5, 136.6, 156.2, 156.6, 169.7, 169.9, 170.0, 170.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{21}NO_5Na$ 330.1317, found 330.1313 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(*N*,4-dimethylphenylsulfonamido)-3-methoxypent-4-enoate (326)



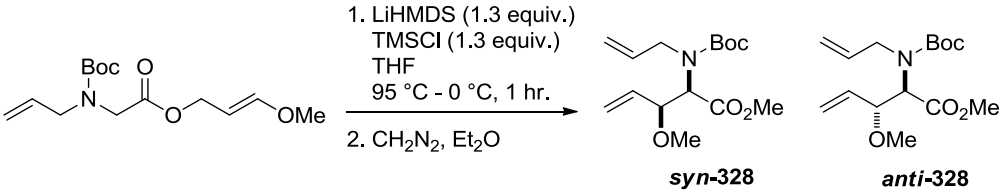
(*E*)-3-Methoxyallyl 2-(*N*,4-dimethylphenylsulfonamido)acetate **309** (0.17 g, 0.53 mmol), TMSCl (0.09 mL, 0.69 mmol) and LiHMDS (0.69 mL, 0.69 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (8:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.12 g, 70% dr 1:1). FTIR (film/cm^{-1}) υ_{max}: 2952.4, 2944.8, 2830.0, 1742.5, 1598.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-326**: 2.43 (s, 3H, CH_3Ph), 2.88 (s, 3H, NCH_3), 3.25 (s, 3H, OCH_3), 3.50 (s, 3H, CO_2CH_3), 3.88 (app. t, 1H, *J* = 9.2 Hz, H_2C=CHC*H*O), 4.59 (d, 1H, *J* = 9.2 Hz, NC*H*CO_2), 5.31 – 5.38 (m, 2H, H_2C=CHCHO), 5.70 – 5.78 (m, 1H, H_2C=C*H*CHO), 7.27 – 7.29 (m, 2H, Ar-*H* Ph), 7.66 – 7.68 (m, 2H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-326**: 21.5, 31.0, 51.9, 56.7, 61.5, 81.7, 120.7, 127.5, 129.4, 134.2, 136.0, 143.4, 169.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{15}H_{21}NO_5Na$ 350.1038, found 350.1026 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 3-methoxy-2-(*N*-methylacetamido)pent-4-enoate (327)



(*E*)-3-Methoxyallyl 2-(*N*-methylacetamido)acetate **310** (0.10 g, 0.48 mmol), TMSCl (0.08 mL, 0.62 mmol) and LiHMDS (0.62 mL, 0.62 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (2:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.06 g, 58%, dr 1:1 obtained as a mixture of 1:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 2992.4, 2974.8, 1724.9, 1587.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-327**: 2.10 & 2.12 (2s, 3H, C*H*$_3$CON), 2.98 & 3.02 (2s, 3H, NC*H*$_3$), 3.30 &3.31 (2s, 3H, OC*H*$_3$), 3.75 & 3.76 (2s, 3H, CO_2CH_3), 4.03 – 4.10 (m, 1H, H_2C=CHC*H*O), 4.29 – 4.38 (m, 1H, NC*H*CO_2), 5.29 – 5.35 (m, 2H, *H*$_2$C=CHCHO), 5.61 – 5.71 (m, 1H, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-327**: 21.4, 33.9, 45.7, 57.7, 60.4, 81.9, 118.4, 133.7, 165.5, 171.5; HRMS (ESI, +ve) *m/z*: calcd. for $C_{10}H_{17}NO_4Na$ 238.1055, found 238`.1062 $(M+Na)^+$.

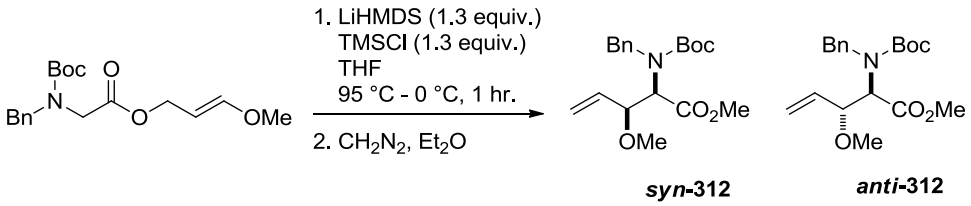
(±)-(2*R*,3*S*)-Methyl 2-(allyl(*tert*-butoxycarbonyl)amino)-3-methoxypent-4-enoate (328)



(*E*)-3-Methoxyallyl 2-(allyl(*tert*-butoxycarbonyl)amino)acetate **311** (0.17 g, 0.59 mmol), TMSCl (0.10 mL, 0.77 mmol) and LiHMDS (0.77 mL, 0.77 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (10:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.13 g, 73%, dr 1:1 obtained as a mixture of 1:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3007.2, 3001.8, 2985.7, 1704.2, 1698.2, 1689.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-328**: 1.43 & 1.45 (2s, 9H, (C*H*$_3$)$_3$COCON), 3.26 (s, 3H, OC*H*$_3$), 3.71 & 3.76 (2s, 3H, CO_2CH_3), 4.03 – 4.10 (m, 1H, H_2C=CHC*H*O), 4.18 – 4.20 (m, 2H, H_2C=CHC*H*$_2$N), 4.31 – 4.35 (m, 1H, NC*H*CO_2), 5.05 – 5.20 (m, 2H, *H*$_2$C=CHCH$_2$N), 5.28 – 5.37 (m, 2H, *H*$_2$C=CHCHO), 5.72 – 5.83 (m, 1H,

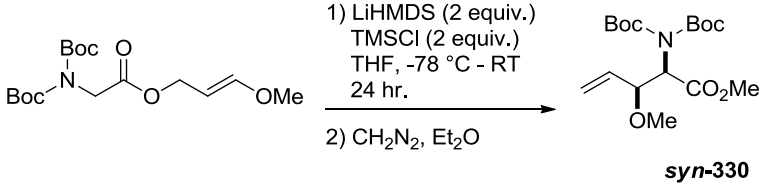
H_2C=C*H*CH_2N), 5.87 – 5.97 (m, 1H, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-328**: 28.3, 50.0, 51.9, 56.7, 61.8, 80.3, 81.5, 115.3, 119.2, 134.5, 136.8, 156.3, 170.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_{15}H_{25}NO_5Na$ 322.1630, found 322.1640 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-3-methoxypent-4-enoate (329)



(*E*)-3-Methoxyallyl 2-(benzyl(*tert*-butoxycarbonyl)amino)acetate **312** (0.12 g, 0.36 mmol), TMSCl (0.06 mL, 0.46 mmol) and LiHMDS (0.46 mL, 0.46 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (10:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.07 g, 57%, dr 4:1 obtained as a mixture of 2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3102.5, 2998.4, 2897.5, 1715.2, 1704.8, 1695.2, 1666.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-312**: 1.36 & 1.47 (2s, 9H, $(CH_3)_3$COCON), 3.17 & 3.22 (2s, 3H, OCH_3), 3.57 & 3.63 (2s, 3H, CO_2CH_3), 4.01 – 4.94 (m, 4H, H_2C=CHC*H*O, NC*H*CO_2 & PhCH_2N), 5.20 – 5.34 (m, 2H, H_2C=CHCHO), 5.61 – 5.75 (m, 1H, H_2C=C*H*CHO), 7.19 – 7.36 (m, 5H, Ar-*H* Ph);^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-312**: 28.1, 47.5, 52.0, 56.6, 62.3, 74.9, 81.1, 119.4, 127.0, 127.8, 128.6, 134.8, 139.7, 156.4, 170.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{19}H_{27}NO_5Na$ 327.1787, found 327.1749 $(M+Na)^+$.

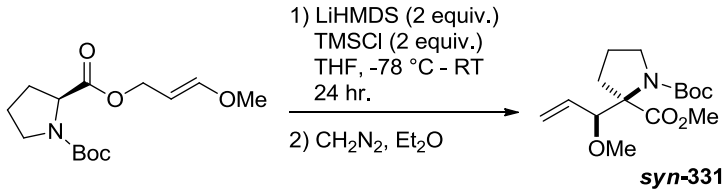
(±)-(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-methoxypent-4-enoate (330)



(*E*)-3-Methoxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **314** (0.10 g, 0.28 mmol), TMSCl (0.07 mL, 0.55 mmol) and LiHMDS (0.55 mL, 0.55 mmol) were combined according to general procedure 7. Treatment with diazomethane and purification by

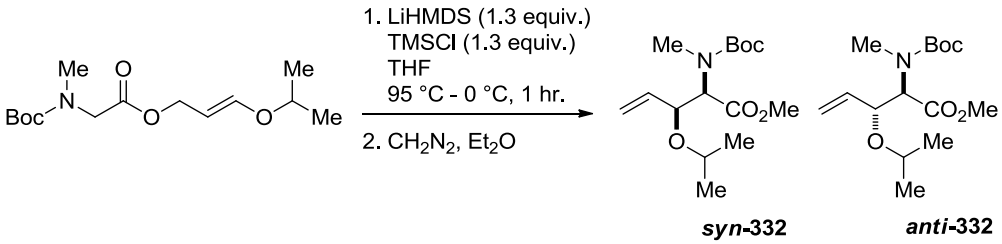
flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.07 g, 72%, as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 2986.3, 2938.0, 1752.4, 1698.1, 1649.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-330**: 1.51 (s, 18H, $(CH_3)_3COCON$), 3.27 (s, 3H, $CHOCH_3$), 3.70 (s, 3H, CO_2CH_3), 4.18 (app. t, 1H, *J* = 7.8 Hz, H_2C=$CHCHOCH_3$), 4.87 (d, 1H, *J* = 7.8 Hz, $NCHCO_2$), 5.33 (dq, 1H, *J* = 10.4, 1.2 Hz, H_2C=$CHCHOCH_3$), 5.42 (dq, 1H, *J* = 17.1, 1.2 Hz, H_2C=$CHCHOCH_3$), 5.88 (ddd, 1H, *J* = 17.1, 10.4, 7.8 Hz, H_2C=$CHCHOCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-330**: 30.0, 52.0, 56.8, 61.4, 79.1, 82.9, 118.6, 136.4, 152.2, 169.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{17}H_{29}NO_7Na$ 382.1842, found 382.1830 $(M+Na)^+$.

(*S*)-1-*tert*-Butyl 2-methyl 2-((*S*)-1-methoxyallyl)pyrrolidine-1,2-dicarboxylate (331)



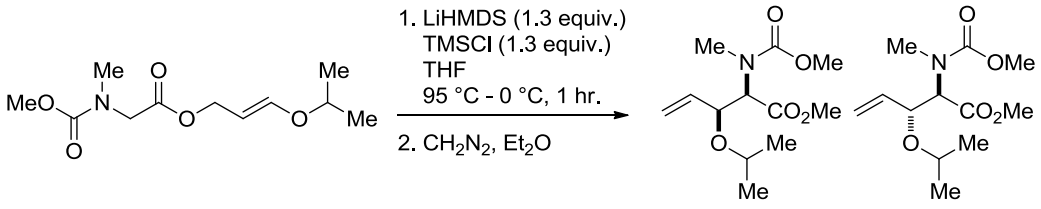
(*S*,*E*)-1-*tert*-Butyl 2-(3-methoxyallyl) pyrrolidine-1,2-dicarboxylate **315** (0.14 g, 0.50 mmol), TMSCl (0.13 mL, 1.00 mmol) and LiHMDS (1.00 mL, 1.00 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.14 g, 95%, as a single diastereomer as a 2:1 mixture of rotamers). FTIR (film/cm^{-1}) υ_{max}: 3001.2, 2988.4, 2875.3, 1715.2, 1698.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-331**: 1.35 & 1.37 (2s, 9H, $(CH_3)_3COCON$), 1.30 – 1.67 (m, 4H, CH_2CH_2CH), 3.16 – 3.75 (m, 2H, NCH_2), 3.23 & 3.25 (2s, 3H, OCH_3), 3.60 & 3.61 (2s, 3H, CO_2CH_3), 4.28 – 4.36 & 4.53 – 4.60 (2m, 1H, H_2C=$CHCHO$), 5.11 – 5.33 (m, 2H, H_2C=$CHCHO$), 5.88 – 6.06 (m, 1H, H_2C=$CHCHO$); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-331**: 23.3, 23.9, 28.8, 30.1, 32.4, 33.9, 18.8, 48.8, 48.9, 52.2, 52.3, 58.3, 58.6, 70.2, 70.7, 79.9, 80.5, 82.0, 117.2, 117.3, 135.6, 135.7, 153.5, 154.3, 173.7 (×2); HRMS (ESI, +ve) *m/z*: calcd. for $C_{15}H_{26}NO_5$ 300.1811, found 300.1801 $(M+H)^+$.

(±)-(2*R*,3*S*)-Methyl 2-((*tert*-butoxycarbonyl)(methyl)amino)-3-isopropoxypent-4-enoate (332)



(*E*)-3-Isopropoxyallyl 2-((*tert*-butoxycarbonyl)(methyl)amino)acetate **320** (0.18 g, 0.62 mmol), TMSCl (0.10 mL, 0.81 mmol) and LiHMDS (0.81 mL, 0.81 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (8:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.10 g, 62%, dr 2:1 obtained as a mixture of 2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 2999.3, 2978.6, 1715.2, 17.04.2, 1659.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***syn*-332**: 1.05 & 1.09 (2d, 6H, OCH(CH_3)$_2$), 1.42 & 1.43 (2s, 9H, (CH_3)$_3$COCON), 2.85 & 2.94 (2s, 3H, NCH_3), 3.57 & 3.67 (2quin, 1H, J = 6.0 Hz, C*H*(CH_3)$_2$), 3.71 (s, 3H, CO_2CH_3), 4.25 – 4.42 (m, 1H, H_2C=CHC*H*O), 4.48 - 4.99 (m, 1H, NC*H*CO_2), 5.19 – 5.34 (m, 2H, H_2C=CHCHO), 5.66 – 5.79 (m, 1H, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***syn*-332**: 21.4, 28.3, 33.1, 51.7, 61.6, 70.5, 79.7, 117.4, 135.7, 156.7, 170.3; HRMS (ESI, +ve) *m/z*: calcd. for $C_{15}H_{27}NO_5Na$ 324.1787, found 324.1770 $(M+Na)^+$.

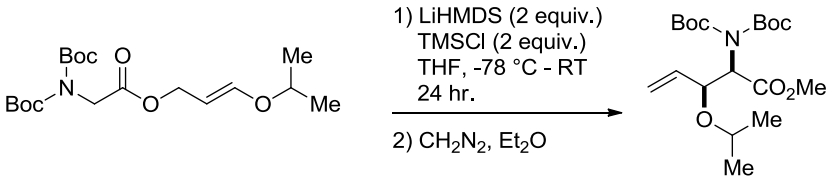
(±)-(2*R*,3*S*)-Methyl 3-isopropoxy-2-((methoxycarbonyl)(methyl)amino)pent-4-enoate (333)



(*E*)-3-Isopropoxyallyl 2-(methoxycarbonyl(methyl)amino)acetate **321** (0.14 g, 0.58 mmol), TMSCl (0.11 mL, 0.85 mmol) and LiHMDS (0.85 mL, 0.85 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (10:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.07 g, 66%, dr 1:1 obtained as a mixture of 2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3001.2, 2988.7, 1704.9, 1659.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 & 1.08 (2d, 6H, *J* = 6.3 Hz, OCH(CH_3)$_2$), 2.87 & 3.00 (2s, 3H, NCH_3),

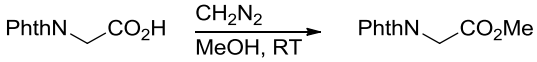
3.65 – 3.67 (m, 1H, OC*H*(CH_3)$_2$), 3.68 (s, 3H, NCO_2CH_3), 3.71 (s, 3H, CO_2CH_3), 4.21 – 4.52 (m, 1H, H_2C=CHC*H*O), 4.54 -5.05 (m, 1H, NC*H*CO_2), 5.22 – 5.34 (m, 2H, H_2C=CHCHO), 5.64 – 5.78 (m, 1H, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 31.5, 32.8, 51.8, 61.5, 70.3, 77.9, 117.7, 135.4, 158.1, 170.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{12}H_{21}NO_5Na$ 282.1317, found 282.1330 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-isopropoxypent-4-enoate (334)



(*E*)-3-Isopropoxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **322** (0.10 g, 0.31 mmol), TMSCl (0.08 mL, 0.61 mmol) and LiHMDS (0.61 mL, 0.61 mmol) were combined according to general procedure 6. Treatment with diazomethane and purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.05 g, 50% as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 2979.2, 2937.1, 1798.7, 1750.2, 1698.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.09 (dd, 6H, *J* = 11.0, 6.1 Hz, OCH(CH_3)$_2$), 1.51 (s, 18H, (CH_3)$_3$COCON), 3.63 (sept, 1H, *J* = 6.1 Hz, OC*H*(CH_3)$_2$), 3.70 (s, 3H, CO_2CH_3), 4.41 – 4.44 (m, 1H, H_2C=CHC*H*OCH_3), 4.80 (d, 1H, *J* = 9.4 Hz, NC*H*CO_2), 5.24 (dq, 1H, *J* = 10.5, 0.8 Hz, H_2C=CHCHO), 5.44 (dq, 1H, *J* = 15.4, 0.8 Hz, H_2C=CHCHO), 6.03 (ddd, 1H, *J* = 15.4, 10.5, 6.3 Hz, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.4, 28.0, 52.1, 62.1, 69.9, 74.9, 83.1, 117.1, 138.1, 152.2, 169.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_{19}H_{33}NO_7Na$ 410.2154, found 410.2144 $(M+Na)^+$.

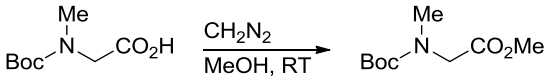
Methyl 2-(1,3-dioxoisoindolin-2-yl)acetate (232)



To a stirred solution of phthaloyl glycine **228** (0.58 g, 2.82 mmol) in methanol (20 mL) was added an ethereal solution of diazomethane until a yellow colour persisted. The reaction was quenched with acetic acid and concentrated *in vacuo*. Purification was achieved by flash chromatography (4:1 Petrol/EtOAc) to afford the title compound as a colourless solid (0.36 g, 58%). MP: 111 – 113 °C, Lit: 112 – 113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.78 (s, 3H, CO_2CH_3), 4.46 (s, 2H, NCH_2CO_2), 7.74 – 7.78 (m, 2H,

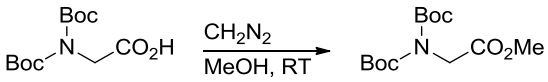
Ar-*H* Phth), 7.88 – 7.91 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 38.8, 52.7, 123.6, 132.1, 134.2, 167.4, 167.7. All data is in accordance with reported literature values.[179]

Methyl 2-((*tert*-butoxycarbonyl)(methyl)amino)acetate (335)



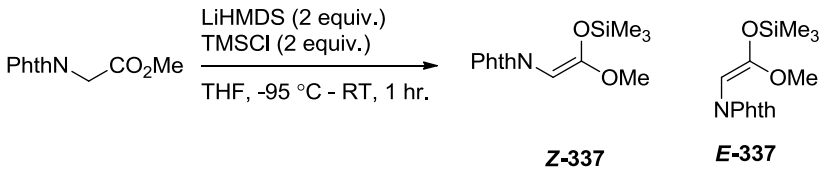
To a stirred solution of Boc-Sar-OH **294** (0.58 g, 3.07 mmol) in methanol (20 mL) was added an ethereal solution of diazomethane until a yellow colour persisted. The reaction was quenched with acetic acid and concentrated *in vacuo*. Purification was achieved by flash chromatography (4:1 Petrol/EtOAc) to afford the title compound as a colourless oil (0.46 g, 74%, 1:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 2977.5, 2933.2, 1752.1, 1694.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.36 & 1.41 (2s, 9H, (C*H*$_3$)$_3$COCON), 2.86 & 2.87 (2s, 3H, NC*H*$_3$), 3.67 & 3.68 (2s, 3H, CO_2CH_3), 3.85 & 3.92 (2s, 2H, NC*H*$_2$CO$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.1, 28.2, 35.4, 50.0, 50.8, 51.8, 80.0, 155.3, 156.0, 170.3; HRMS (ESI, +ve) *m/z*: calcd. for $C_9H_{18}NO_4$ 204.1236, found 204.1243 $(M+H)^+$.

Methyl 2-(bis(*tert*-butoxycarbonyl) amino)acetate (336)



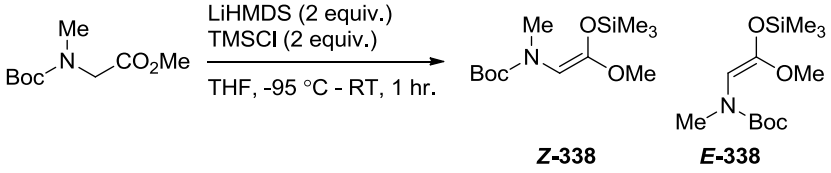
To a stirred solution of di-(*tert*-butoxycarbonyl)aminoacetic acid **305** (0.60 g, 2.18 mmol) in methanol (20 mL) was added an ethereal solution of diazomethane until a yellow colour persisted. The reaction was quenched with acetic acid and concentrated *in vacuo*. Purification was achieved by flash chromatography (1:1 Petrol/EtOAc) to afford the title compound as a colourless oil (0.34 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42 (s, 18H, (C*H*$_3$)$_3$COCON), 3.66 (s, 3H, CO_2CH_3), 4.25 (s, 2H, NC*H*$_2$CO$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.9, 47.0, 51.9, 82.9, 151.8, 169.5. All data is in accordance with reported literature values.[179]

(*Z*)-2-(2-Methoxy-2-((trimethylsilyl)oxy)vinyl)isoindoline-1,3-dione (337)



To a stirred solution of methyl 2-(1,3-dioxoisoindolin-2-yl)acetate **232** (0.05 g, 0.24 mmol, 1 equiv.) in THF (0.5 mL) at -95 °C was added TMSCl (0.06 mL, 0.48 mmol, 2 equiv.) and stirred for 10 minutes. LiHMDS (1M in THF, 0.48 mL, 0.48 mmol, 2 equiv.) was added *via* syringe pump and then the solution was allowed to warm to room temperature. Rapid concentration *in vacuo* afforded the title compound as a yellow solid (0.06 g, 87%, *Z*/*E* 12:1). FTIR (film/cm^{-1}) υ_{max}: 3119.3, 3024.9, 2977.4, 1780.6, 1719.1, 1669.9, 1659.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ ***Z*-337**: 0.22 (s, 9H, NCH=C(OSi(C*H*$_3$)$_3$)OCH$_3$)), 3.80 (s, 3H, NCH=C(OSi(CH$_3$)$_3$)OC*H*$_3$), 4.69 (s, 1H, NC*H*=C(OSi(CH$_3$)$_3$)OCH$_3$), 7.73 – 7.75 (m, 2H, Ar-*H* Phth), 7.88 – 7.90 (m, 2H, Ar-*H* Phth); δ ***E*-337**: 0.22 (s, 9H, NCH=C(OSi(C*H*$_3$)$_3$)OCH$_3$)), 3.81 (s, 3H, NCH=C(OSi(CH$_3$)$_3$)OC*H*$_3$), 4.74 (s, 1H, NC*H*=C(OSi(CH$_3$)$_3$)OCH$_3$), 7.73 – 7.75 (m, 2H, Ar-*H* Phth), 7.88 – 7.90 (m, 2H, Ar-*H* Phth); ^{13}C NMR (100 MHz, $CDCl_3$) δ ***Z*-337**: 5.5, 55.5, 71.8, 123.1, 132.4, 133.8, 159.6, 168.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{14}H_{17}NO_4SiNa$ 314.0825, found 314.0837 $(M+Na)^+$.

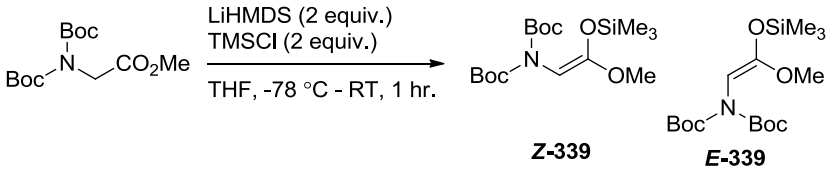
(*Z*)-*tert*-Butyl (2-methoxy-2-((trimethylsilyl)oxy)vinyl)(methyl)carbamate (338)



To a stirred solution of methyl 2-((*tert*-butoxycarbonyl)(methyl)amino)acetate **235** (0.06 g, 0.26 mmol, 1 equiv.) in THF (0.5 mL) at -95 °C was added TMSCl (0.06 mL, 0.52 mmol, 2 equiv.) and stirred for 10 minutes. LiHMDS (1M in THF, 0.52 mL, 0.52 mmol, 2 equiv.) was added *via* syringe pump and then the solution was allowed to warm to room temperature. Rapid concentration *in vacuo* afforded the title compound as a yellow oil (0.05 g, 81%, *Z*/*E* 2:1, 2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 2955.1, 1756.9, 1698.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ ***Z*-338**: 0.22 & 0.26 (2s, 9H, NCH=C(OSi(C*H*$_3$)$_3$)OCH$_3$) 1.49 & 1.51 (2s, 9H, (C*H*$_3$)$_3$COCON), 2.99 & 3.00 (2s, 3H, C*H*$_3$N), 3.58 & 3.60 (2s, 3H, NCH=C(OSi(CH$_3$)$_3$)OC*H*$_3$), 4.88 & 4.93 (2br, 1H, NC*H*=C(OSi(CH$_3$)$_3$)OCH$_3$); δ ***E*-338**: 0.22 & 0.26 (2s, 9H, NCH=C(OSi(C*H*$_3$)$_3$)OCH$_3$)

1.49 & 1.51 (2s, 9H, (C*H*$_3$)$_3$COCON), 2.99 & 3.00 (2s, 3H, C*H*$_3$N), 3.58 & 3.60 (2s, 3H, NCH=C(OSi(CH$_3$)$_3$)OC*H*$_3$), 4.99 & 5.08 (2br, 1H, NC*H*=C(OSi(CH$_3$)$_3$)OCH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ ***Z*-338**: 5.5, 28.5, 55.2, 87.7, 164.1, 179.3; HRMS (ESI, +ve) *m/z*: calcd. for $C_{12}H_{25}NO_4SiNa$ 276.1631, found 276.1627 $(M+Na)^+$.

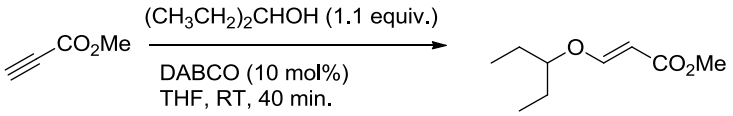
(*Z*)-Bis(*tert*-butyl (2-methoxy-2-((trimethylsilyl)oxy)vinyl))carbamate (339)



***Z*-339** ***E*-339**

To a stirred solution of methyl 2-(bis(*tert*-butoxycarbonyl) amino)acetate (0.06 g, 0.22 mmol, 1 equiv.) in THF (0.5 mL) at -78 °C was added TMSCl (0.06 mL, 0.44 mmol, 2 equiv.) and stirred for 10 minutes. LiHMDS (1M in THF, 0.44 mL, 0.44 mmol, 2 equiv.) was added *via* syringe pump and then the solution was allowed to warm to room temperature. Rapid concentration *in vacuo* afforded the title compound as a yellow oil (0.05 g, 51%, *Z*/*E* >25:1). FTIR (film/cm^{-1}) υ_{max}: 2980.5, 2900.9, 1736.9, 1739.8, 1700.0; ^{1}H NMR (400 MHz, CDCl$_3$) δ ***Z*-339**: 0.19 (s, 9H, NCH=C(OSi(C*H*$_3$)$_3$)OCH$_3$), 1.47 (s, 18H, (C*H*$_3$)$_3$COCON), 3.72 (s, 3H, NCH=C(OSi(CH$_3$)$_3$)OC*H*$_3$), 4.33 (s, 1H, NC*H*=C(OSi(CH$_3$)$_3$)OCH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ ***Z*-339**: 5.6, 28.1, 55.2, 81.7, 156.9, 168.1, 178.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{31}NO_6SiNa$ 314.0825, found 314.0837 $(M+Na)^+$.

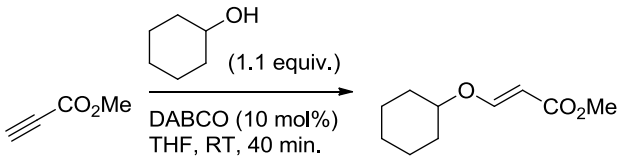
(*E*)-Methyl 3-(pentan-3-yloxy)acrylate (340)



DABCO (0.26 g, 2.38 mmol) in THF (40 mL), 3-pentanol (2.09 g, 2.62 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (12:1 Pet/EtOAc) to afford the title compound as a colourless oil (3.05 g, 75%). FTIR (film/cm^{-1}) υ_{max}: 2971.6, 2944.9, 2881.6 2846.7, 1713.4, 1641.7; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 0.90 (t, 6H, *J* = 7.6 Hz, (C*H*$_3$CH$_2$)$_2$CHO), 1.61 (quin, 4H, *J* = 7.6 Hz, (CH$_3$C*H*$_2$)$_2$CHO), 3.68 (s, 3H, CO$_2$C*H*$_3$), 3.75 (quin, 1H, *J* = 7.6 Hz, (CH$_3$CH$_2$)$_2$C*H*O), 5.23 (d, 1H, *J* = 12.8 Hz, OCH=C*H*CO$_2$CH$_3$), 7.53 (d, 1H, *J* = 12.8 Hz, OC*H*=CHCO$_2$CH$_3$); ^{13}C NMR (125

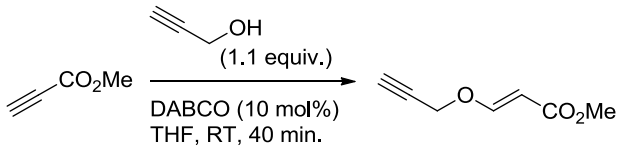
MHz, $CDCl_3$) δ: 9.5, 26.7, 50.9, 86.9, 96.4, 163.1, 168.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_9H_{16}O_3Na$ 195.0992, found 195.0997 $(M+Na)^+$.

(*E*)-Methyl 3-(cyclohexyloxy)acrylate (341)



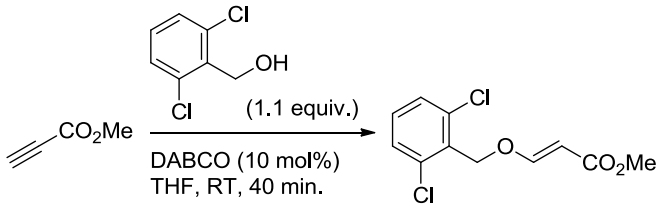
DABCO (0.27 g, 2.38 mmol) in THF (300 mL), cyclohexanol (2.62 g, 26.2 mmol) and methyl propiolate **232** (2.12 mL, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (20:1 Pet/EtOAc) to afford the pure title compound as a colourless oil (0.99 g, 23%). FTIR (film/cm^{-1}) υ_{max}: 2937.0, 2860.6, 1707.3, 1638.3, 1619.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.23 – 1.56 (m, 6H, Cy-*H*), 1.72 – 1.76 (m, 2H, Cy-*H*), 1.89 – 1.93 (m, 2H, Cy-*H*), 3.69 (s, 3H, CO_2CH_3), 3.93 (sept, 1H, *J* = 4.1 Hz, C*H*OCH=CHCO$_2$CH$_3$), 5.25 (d, 1H, *J* = 12.7 Hz, OCH=C*H*CO$_2$), 7.56 (d, 1H, *J* = 12.7 Hz, OC*H*=CHCO$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.4, 25.2, 31.8, 51.0, 81.0, 96.8, 161.8, 168.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_{10}H_{16}O_3Na$ 207.0997, found 207.0994 $(M+Na)^+$.

(*E*)-Methyl 3-(prop-2-ynyloxy)acrylate (342)



DABCO (0.40 g, 3.57 mmol) in THF (300 mL), propagylic alcohol (2.3 mL, 3.93 mmol) and methyl propiolate **232** (3.2 mL, 35.7 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colourless oil (5.10 g, 98%). FTIR (film/cm^{-1}) υ_{max}: 3293.2, 3096.0, 2998.8, 2953.6, 2124.5, 1704.9, 1646.0, 1624.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.60 (t, 1H, *J* = 2.6 Hz, *H*C≡CCH$_2$O), 3.71 (s, 3H, CO_2CH_3), 4.53 (d, 2H, *J* = 2.6 Hz, HC≡CC*H*$_2$O), 5.35 (d, 1H, *J* = 12.7 Hz, OCH=C*H*CO$_2$CH$_3$), 7.58 (d, 1H, *J* = 12.7 Hz, OC*H*=CHCO$_2$CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.2, 58.1, 76.6, 77.0, 98.3, 160.6, 167.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_7H_8O_3Na$ 163.0371, found 163.0364 $(M+Na)^+$.

(*E*)-Methyl 3-(2,6-dichlorobenzyloxy)acrylate (343)

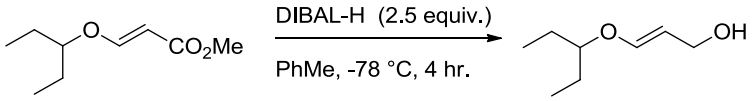


DABCO (0.27 g, 23.8 mmol) in THF (300 mL), 2,6-dichlorobenzyl alcohol (4.63 g, 26.2 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (10:1 Pet/EtOAc) to afford title compound as a colourless oil (3.82 g, 62%). FTIR (film/cm^{-1}) υ_{max}: 3090.0, 2951.1, 2892.8, 1706.6, 1644.1, 1620.7, 1583.0, 1565.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.73 (s, 3H, CO_2CH_3), 5.16 (s, 2H, $ArCH_2O$), 5.39 (d, 1H, *J* = 12.6 Hz, $OCH=CHCO_2CH_3$), 7.25 – 7.28 (m, 1H, Ar-*H* Ph) 7.35 (s, 1H, Ar-*H* Ph), 7.37 (s, 1H, Ar-*H* Ph), 7.71 (d, 1H, *J* = 12.6 Hz, $OCH=CHCO_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.2, 67.5, 97.1, 128.5, 130.7, 131.0, 137.0, 162.1, 167.9; HRMS (ESI, +ve) *m/z*: calcd. for $C_{11}H_{10}Cl_2O_3Na$ 282.9905, found 282.9887 $(M+Na)^+$.

(*S*,*E*)-Methyl 3-(1-phenylethoxy)acrylate (344)

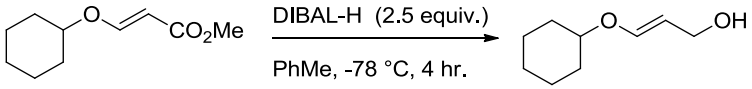
DABCO (0.26 g, 2.38 mmol) in THF (200 mL), (*S*)-1-phenylethanol (2.90 g, 26.2 mmol) and methyl propiolate **232** (2.00 g, 23.8 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (30:1 Pet/EtOAc) to afford the title compound as a white solid (4.0 g, 81%). $[\alpha]_D^{20}$ = -113° (*c* 1, DCM); MP: 38 – 39 °C; FTIR (film/cm^{-1}) υ_{max}: 2993.6, 2950.2, 1713.4, 1643.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.60 (d, 3H, *J* = 7.2 Hz, $OCH(CH_3)Ph$), 3.65 (s, 3H, CO_2CH_3), 5.04 (q, 1H, *J* = 7.2 Hz, $OCH(CH_3)Ph$), 5.25 (d, 1H, *J* = 12.5 Hz, OCHCHC(O)), 7.39 – 7.29 (m, 5H, Ar-*H* Ph), 7.52 (d, 2H, *J* = 12.5 Hz, OCHCHC(O)); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.4, 51.0, 80.5, 98.1, 125.7, 128.2, 128.8, 141.2, 161.5, 168.2; HRMS (ESI, +ve) *m/z* calcd. for $C_{12}H_{14}O_3Na$ 229.0841, found 229.0832. $(M+Na)^+$.

(*E*)-3-(pentan-3-yloxy)prop-2-enol (345)



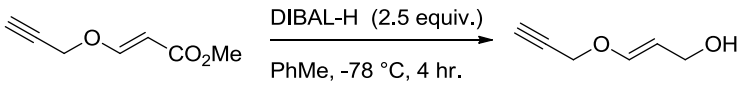
(*E*)-Methyl 3-(pentan-3-yloxy)acrylate **340** (1.32 g, 10.4 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil. (1.05 g, 68%). FTIR (film/cm^{-1}) υ_{max}: 3347.2, 2966.1, 2937.3, 2878.9, 1699.1, 1650.3. ^{1}H NMR (500 MHz, d_6-acetone) δ: 0.89 (t, 6H, *J* = 7.4 Hz, (C*H*$_3$CH$_2$)$_2$CHO), 1.55 (m, 4H, (CH$_3$C*H*$_2$)$_2$CHO), 3.31 (t, 1H, *J* = 5.8 Hz, OCH=CHCH$_2$O*H*), 3.54 (quin, 1H, *J* = 5.9 Hz, (CH$_3$CH$_2$)$_2$C*H*O), 4.00 (dd, 2H, *J* = 7.6, 1.0 Hz, OCH=CHC*H*$_2$OH), 5.08 (dt, 1H, *J* = 12.3, 7.6 Hz, OCH=C*H*CH$_2$OH), 6.37 (d, 1H, *J* = 12.3 Hz, OC*H*=CHCH$_2$OH). ^{13}C NMR (125 MHz, d_6-acetone) δ: 8.9, 26.2, 59.4, 82.8, 104.7, 148.8.

(*E*)-3-(Cyclohexyloxy)prop-2-en-1-ol (346)



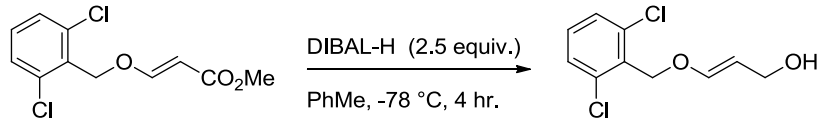
(*E*)-Methyl 3-(cyclohexyloxy)acrylate **341** (0.84 g, 4.55 mmol) was reduced according to the general procedure 5 to afford the title compound as a yellow oil (0.53 g, 74%). FTIR (film/cm^{-1}) υ_{max}: 3338.1, 2932.0, 2858.9, 1669.8, 1649.4; ^{1}H NMR (500 MHz, d_6-acetone) δ: 1.21 – 1.56 (m, 6H, Cy-*H*), 1.67 – 1.77 (m, 2H, Cy-*H*), 1.79 – 1.91 (m, 2H, Cy-*H*), 3.27 (t, 1H, *J* = 5.6 Hz,OCH=CHCH$_2$O*H*), 3.71 – 3.79 (m, 1H, OC*H*), 3.91 – 3.97 (m, 2H, OCH=CHC*H*$_2$OH), 5.01 (dt, 1H, *J* = 12.4, 7.2 Hz, OCH=C*H*CH$_2$OH), 6.39 (d, 1H, *J* = 12.4 Hz, OC*H*=CH$_2$OH); ^{13}C NMR (125 MHz, d_6-acetone) δ: 23.3, 25.3, 31.8, 59.3, 77.4, 105.1, 147.6.

(*E*)-3-(Prop-2-ynyloxy)prop-2-en-1-ol (347)



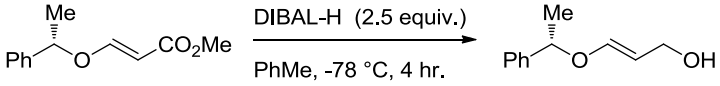
(*E*)-Methyl 3-(prop-2-ynyloxy)acrylate **342** (1.03 g, 7.35 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (0.63 g, 75%). FTIR (film/cm^{-1}) υ_{max}: 3380.5, 3289.2, 2926.0, 2869.7, 2120.7, 1671.8, 1653.0; ^{1}H NMR (500 MHz, d_6-acetone) δ: 2.60 (dt, 1H, *J* = 2.4, 0.8 Hz, *H*C≡CCH$_2$O), 4.06 (d, 2H, *J* = 7.2 Hz, OCH=CHC*H*$_2$OH), 4.43 (d, 2H, *J* = 2.4 Hz, HC≡CC*H*$_2$O), 5.17 (dt, 1H, *J* = 12.7, 7.2 Hz, OCH=C*H*CH$_2$OH), 6.52 (d, 1H, *J* = 12.7 Hz, OC*H*=CHCH$_2$OH); ^{13}C NMR (125 MHz, d_6-acetone) δ: 57.0, 60.1, 75.3, 78.5, 105.4, 148.1.

(*E*)-3-(2,6-Dichlorobenzyloxy)prop-2-en-1-ol (348)



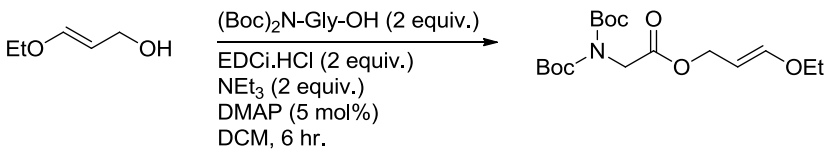
(*E*)-Methyl 3-(2,6-dichlorobenzyloxy)acrylate **343** (1.25 g, 4.79 mmol) was reduced according to the general procedure to afford the title compound as a white solid (0.74 g, 67%). MP: 80 – 83 °C; FTIR (film/cm^{-1}) υ_{max}: 3300.2, 3078.3, 2945.4, 2863.0, 1672.2, 1583.1, 1563.1; ^{1}H NMR (500 MHz, d_6-acetone) δ: 3.46 (t, 1H, *J* = 5.6 Hz, OCH=CHCH$_2$O*H*), 4.02 (m, 2H, OCH=CHC*H*$_2$OH), 5.03 (s, 2H, ArC*H*$_2$O), 5.18 (dt, 1H, *J* = 12.6, 7.2 Hz, OCH=C*H*CH$_2$OH), 6.63 (d, 1H, *J* = 12.6 Hz, OC*H*=CHCH$_2$OH), 7.41 – 7.45 (m, 1H, Ar-*H* Ph), 7.49 – 7.51 (m, 2H, Ar-*H* Ph); ^{13}C NMR (125 MHz, d_6-acetone) δ: 59.2, 65.5, 104.8, 128.6, 131.0, 132.4, 136.5, 148.2.

(*S*,*E*)-3-(1-phenylethoxy)prop-2-enol (349)



(*S*,*E*)-Methyl 3-(1-phenylethoxy)acrylate **344** (2.65 g, 12.9 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (1.72 g, 75%). $[\alpha]_D^{20}$ -68° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 3347.2, 3086.6, 3062.8, 3031.0, 2977.6, 2930.0, 2872.4, 1670.1, 1671.2, 1651.2; ^{1}H NMR (500 MHz, d_6-DMSO) δ: 1.42 (d, 3H, *J* = 6.5 Hz, PhCH(C*H*$_3$)O), 3.75 (app. t, 2H, *J* = 6.6 Hz, OCH=CHC*H*$_2$OH), 4.38 (t, 1H, *J* = 5.4 Hz, OCH=CHCH$_2$O*H*), 4.88 – 4.95 (m, 2H, OCH=CCH$_2$OH & PhC*H*(CH$_3$)O), 6.33 (d, 1H, *J* = 12.4 Hz, OC*H*=CHCH$_2$OH), 7.30 – 7.38 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, d_6-DMSO) δ: 23.8, 58.8, 77.7, 106.6, 126.3, 127.9, 128.9, 143.4, 147.4.

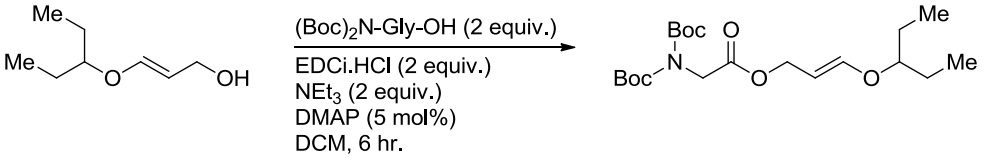
(*E*)-3-Ethyloxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (350)



EDCi.HCl (0.75 g, 3.91 mmol), triethylamine (0.54 mL, 3.91 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (1.07 g, 3.91 mmol) , catalytic DMAP and (*E*)-3-ethoxyprop-2-enol **247** (0.20 g, 1.96 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (0.64 g, 91%). FTIR (film/cm^{-}

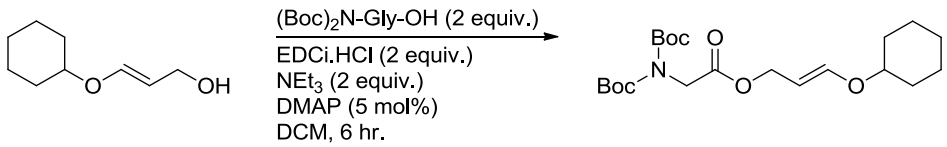
[1]) υ_{max}: 2980.6, 2935.6, 1755.7, 1743.7, 1697.4, 1652.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.20 (t, 3H, *J* = 6.8 Hz, OCH_2CH_3), 1.43 (s, 18H, $(CH_3)_3COCON$), 3.69 (q, 2H, *J* = 6.8 Hz, OCH_2CH_3), 4.23 (s, 2H, NCH_2CO_2), 4.48 (d, 2H, *J* = 7.9 Hz, CO_2CH_2CH=CHO), 4.85 (dt, 1H, *J* = 12.7, 7.9 Hz, CO_2CH_2CH=CHO), 6.51 (d, 1H, *J* = 12.7 Hz, CO_2CH_2CH=C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.5, 27.9, 47.3, 63.4, 64.9, 82.8, 97.2, 151.7, 152.7, 169.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{17}H_{29}NO_7Na$ 382.1842, found 382.1853 $(M+Na)^+$.

(*E*)-3-(Pentan-3-yloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (351)



EDCi.HCl (0.62 g, 3.23 mmol), triethylamine (0.45 mL, 3.23 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.89 g, 3.23 mmol), catalytic DMAP and (*E*)-3-(pentan-3-yloxy)prop-2-enol **345** (0.24 g, 1.62 mmol) were combined according to general procedure 3 omitting the citric acid wash, to afford the title compound as a brown oil (0.49 g, 75%). FTIR (film/cm^{-1}) υ_{max}: 2978.7, 2937.9, 2881.5, 1798.9, 1755.9, 1736.3, 1697.7, 1669.7; ^{1}H NMR (500 MHz, d_6-acetone) δ: 0.90 (t, 6H, *J* = 7.5 Hz, $(CH_3CH_2)_2CHO$), 1.49 – 1.50 (m, 22H, $(CH_3)_3COCON$) & $(CH_3CH_2)_2CHO$)), 3.70 (quin, 1H, *J* = 5.8 Hz, $(CH_3CH_2)_2CHO$), 4.28 (s, 2H, NCH_2CO_2), 4.55 (d, 2H, *J* = 7.9 Hz, OCH_2CH=CHO), 4.99 (dt, 1H, *J* = 12.2, 7.9 Hz, OCH_2CH=CHO), 6.66 (d, 1H, *J* = 12.2 Hz, OCH_2CH=C*H*O); ^{13}C NMR (125 MHz, d_6-acetone) δ: 8.9, 26.3, 27.3, 47.1, 63.2, 82.1, 83.6, 98.2, 151.8, 153.2, 168.9; HRMS (ESI, +ve) *m/z*: calcd. for $C_{20}H_{35}NO_7Na$ 424.2311, found 424.2349 $(M+Na)^+$.

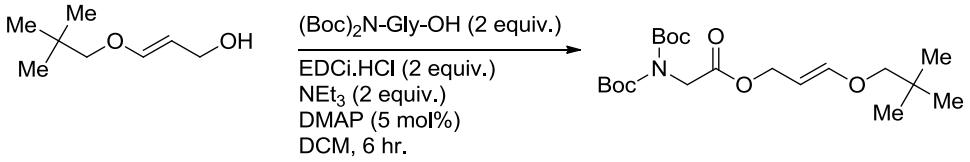
(*E*)-3-(Cyclohexyloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (352)



EDCi.HCl (0.49 g, 2.56 mmol), triethylamine (0.36 mL, 2.56 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.70 g, 2.56 mmol), catalytic DMAP and (*E*)-3-(cyclohexyloxy)prop-2-en-1-ol **346** (0.20 g, 1.28 mmol) were combined according to general procedure 3 omitting the citric acid wash, to afford the title compound as a brown oil (0.26 g, 45%). FTIR (film/cm^{-1}) υ_{max}: 2998.3, 2996.2, 1798.6, 1736.9, 1697.5,

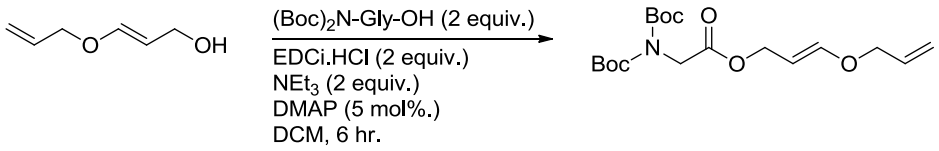
1667.3; ^{1}H NMR (500 MHz, d_6-acetone) δ: 1.21 – 1.56 (m, 24H, (CH_3)$_3$COCON & Cy-*H*), 1.67 – 1.77 (m, 2H, Cy-*H*), 1.79 – 1.91 (m, 2H, Cy-*H*), 3.81 – 3.86 (m, 1H, OC*H*), 4.27 (s, 2H, NCH_2CO$_2$), 4.54 (d, 2H, *J* = 7.9 Hz, OCH_2CH=CHO), 5.00 (dt, 1H, *J* = 12.4, 7.9 Hz, OCH$_2$C*H*=CHO), 6.65 (d, 1H, *J* = 12.4 Hz, OCH$_2$CH=C*H*O); ^{13}C NMR (125 MHz, d_6-acetone) δ: 23.3, 25.2, 27.3, 31.7, 47.1, 63.1, 78.2, 82.1, 98.6, 151.8, 151.9, 168.9; HRMS (ESI, +ve) *m/z*: calcd. for $C_{21}H_{35}NO_7Na$ 436.2311, found 436.2319 $(M+Na)^+$.

(*E*)-3-(Neopentyloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (353)



EDCi.HCl (0.45 g, 2.33 mmol), triethylamine (0.32 mL, 2.33 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.64 g, 2.33 mmol), catalytic DMAP and (*E*)-3-(neopentyloxy)prop-2-en-1-ol **250** (0.17 g, 1.16 mmol) were combined according to general procedure 3 to afford the title compound as a yellow oil (0.33 g, 71%). FTIR (film/cm^{-1}) υ_{max}: 2979.9, 2868.7, 1796.5, 1756.3, 1736.1, 1698.4, 1651.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.92 (s, 9H, OCH$_2$C(CH_3)$_3$), 1.48 (s, 18H, (CH_3)$_3$COCON), 3.32 (s, 2H, OCH_2C(CH$_3$)$_3$), 4.28 (s, 2H, NCH_2CO$_2$), 4.55 (d, 2H, *J* = 7.8 Hz, OCH_2CH=CHO), 4.89 (dt, 1H, *J* = 12.6, 7.8 Hz, OCH$_2$C*H*=CHO), 6.61 (d, 1H, *J* = 12.6 Hz, OCH$_2$CH=C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.4, 28.0, 43.0, 47.4, 63.6, 79.3, 82.9, 96.6, 151.8, 153.6, 169.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{20}H_{35}NO_7Na$ 424.2311, found 424.2299 $(M+Na)^+$.

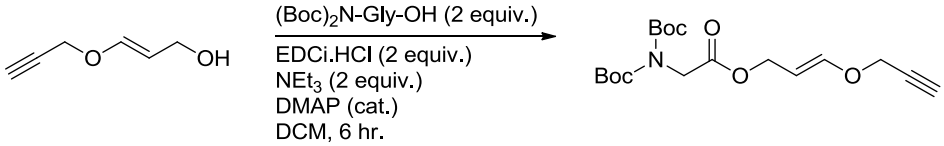
(*E*)-3-(Allyloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (354)



EDCi.HCl (0.53 g, 2.76 mmol), triethylamine (0.40 mL, 2.76 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.76 g, 2.76 mmol), catalytic DMAP and (*E*)-3-(allyloxy)prop-2-enol **251** (0.16 g, 1.38 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (0.40 g, 78%). FTIR (film/cm^{-1}) υ_{max}: 2981.3, 2936.0, 1755.8, 1735.8, 1698.0, 1673.1, 1654.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.51 (s, 18H, (CH_3)$_3$COCON), 4.26 (dt, 2H, *J* = 5.6, 1.5 Hz, OCH_2CH=CH$_2$)

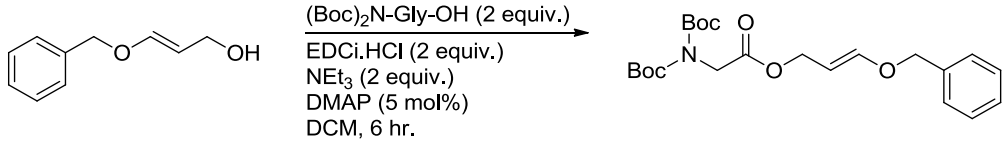
4.32 (s, 2H, NCH_2CO_2), 4.58 (d, 2H, J = 7.8 Hz, OCH_2CH=CHO), 4.99 (dt, 1H, J = 12.7, 7.8 Hz, OCH$_2$CH=CHO), 5.26 (dq, 1H, J = 10.5, 1.5 Hz, OCH$_2$CH=CH_2), 5.34 (dq, 1H, J = 17.2, 1.5 Hz, OCH$_2$CH=CH_2), 5.90 – 5.98 (m, 1H, OCH$_2$CH=CH$_2$), 6.60 (d, 1H, J = 12.7 Hz, OCH$_2$CH=CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0, 47.4, 63.4, 70.3, 83.0, 98.1, 118.0, 132.7, 151.9, 152.3, 169.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{18}H_{29}NO_7Na$ 394.1842, found 394.1831 $(M+Na)^+$.

(*E*)-3-(prop-2-yn-1-yloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (355)



EDCi.HCl (1.09 g, 5.69 mmol), triethylamine (0.80 mL, 5.69 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (1.57 g, 5.69 mmol), catalytic DMAP and (*E*)-3-(prop-2-yn-1-yloxy)prop-2-en-1-ol **347** (0.32 g, 2.84 mmol) were combined according to general procedure 3, to afford the title compound as a yellow oil (0.90 g, 85%). FTIR (film/cm^{-1}) υ_{max}: 2980.4, 2940.0, 2146.1, 1796.1, 1753.6, 1734.5, 1696.5, 1654.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.47 (s, 18H, CH_3)$_3$COCON), 2.52 (t, 1H, J = 2.5 Hz, OCH$_2$C≡CH), 4.28 (s, 2H, NCH_2CO_2), 4.36 (d, 2H, J = 2.5 Hz, OCH_2C≡CH), 4.55 (dd, 2H, J = 7.9, 0.6 Hz, OCH_2CH=CHO), 5.05 (dt, 1H, J = 12.7, 7.9 Hz, OCH$_2$CH=CHO), 6.55 (d, 1H, J = 12.7 Hz, OCH$_2$CH=CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.9, 47.3, 57.0, 62.9, 75.9, 77.7, 83.0, 99.5, 150.9, 151.8, 169.1; HRMS (ESI, +ve) *m/z* calcd. for $C_{18}H_{27}NO_7Na$ 392.1685, found 392.1705 $(M+Na)^+$.

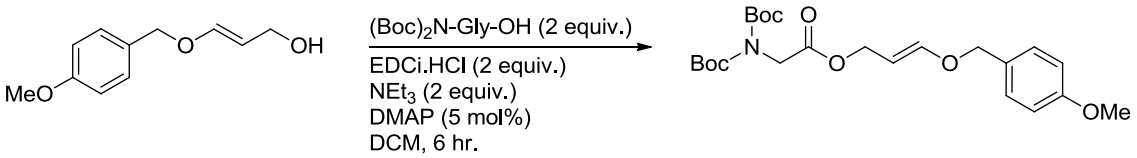
(*E*)-3-(Benzyloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (356)



EDCi.HCl (0.94 g, 4.90 mmol), triethylamine (0.70 mL, 4.90 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (1.35 g, 4.90 mmol), catalytic DMAP and (*E*)-3-bezyloxyprop-2-enol **252** (0.20 g, 2.45 mmol) were combined according to general procedure 3. Purifcation was achieved by flash chromatography (Al_2O, 10:1 Petrol/EtOAc) to afford the title compound as a colourless oil (0.32 g, 63%) FTIR (film/cm^{-1}) υ_{max}: 2980.4, 2938.6, 1757.7, 1736.4, 1698.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.51 (s, 18H, (CH_3)$_3$COCON), 4.33 (s, 2H, NCH_2CO_2), 4.60 (d, 2H, J = 7.8 Hz,

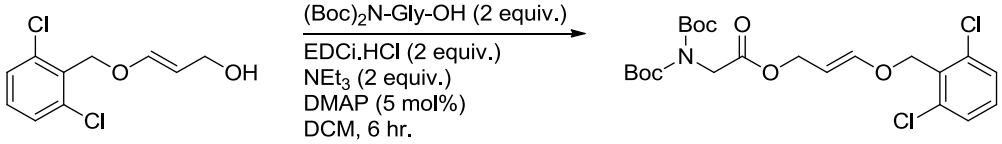
OCH_2CH=CHO), 4.78 (s, 2H, PhCH_2O), 5.08 (dt, 1H, *J* = 12.4, 7.8 Hz, OCH$_2$C*H*=CHO), 6.71 (d, 1H, *J* = 12.4 Hz, OCH$_2$CH=C*H*O), 7.33 – 7.41 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0, 47.4, 63.4, 71.4, 83.1, 98.2, 127.7, 128.2, 128.6, 136.2, 151.9, 152.5, 169.2; HRMS (ESI, +ve) *m/z* calcd. for $C_{22}H_{31}NO_7Na$ 444.1998, found 444.1996 $(M+Na)^+$.

(*E*)-3-(4-Methoxybenzyloxy)allyl 2-(bis(tert-butoxycarbonyl)amino)acetate (357)



EDCi.HCl (0.44 g 2.31 mmol), triethylamine (0.32 mL, 2.31 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.64 g, 2.31 mmol), catalytic DMAP and (*E*)-3-((4-methoxybenzyl)oxy)prop-2-en-1-ol **252** (0.22 g, 1.15 mmol) were combined according to general procedure 3 to afford the title compound as a yellow oil (0.73 g, 70%). FTIR (film/cm^{-1}) υ_{max}: 3054.2, 3026.5, 2998.7, 2968.1, 1759.6, 1731.9, 1698.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.49 (s, 18H, (CH_3)$_3$COCON), 3.80 (s, 3H, ArOCH_3), 4.31 (s, 2H, NCH_2CO$_2$), 4.57 (d, 2H, *J* = 7.6 Hz, OCH_2CH=CHO), 4.68 (s, 2H, OCH_2Ar), 5.04 (dt, 1H, *J* = 12.6, 7.6 Hz, OCH$_2$C*H*=CHO), 6.66 (d, 1H, *J* = 12.6 Hz, OCH$_2$CH=C*H*O), 6.86 – 6.90 (m, 2H, Ar-*H* Ph), 7.24 – 7.29 (m, 2H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0, 47.4, 55.3, 63.4, 71.2, 83.0, 98.1, 114.0, 128.3, 129.4, 151.9, 152.5, 159.6, 169.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{23}H_{33}NO_7Na$ 474.2104, found 474.2123 $(M+Na)^+$.

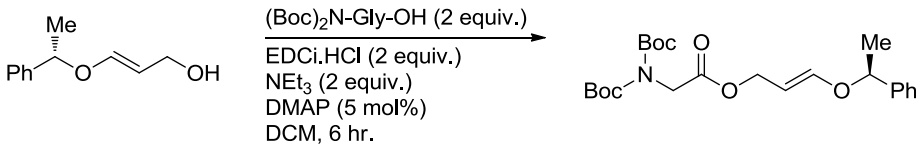
(*E*)-3-((2,6-dichlorobenzyl)oxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (358)



EDCi.HCl (0.55 g, 2.87 mmol), triethylamine (0.40 mL, 2.87 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.79 g, 2.87 mmol), catalytic DMAP and (*E*)-3-(2,6-dichlorobenzyloxy)prop-2-enol **348** (0.34 g, 1.43 mmol) were combined according to general procedure 3 to afford the title compound as a yellow oil (0.74 g, 94%). FTIR (film/cm^{-1}) υ_{max}: 2980.9, 2939.7, 2887.4, 1754.9, 1735.3, 1696.7, 1651.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.52 (s, 18H, (CH_3)$_3$COCON), 4.34 (s, 2H, NCH_2CO$_2$), 4.62 (d, 2H, *J* = 8.8 Hz, OCH_2CH=CHOAr), 5.03 (s, 2H, OCH_2Ar), 5.13 (dt, 1H, *J* = 12.7, 7.8 Hz,

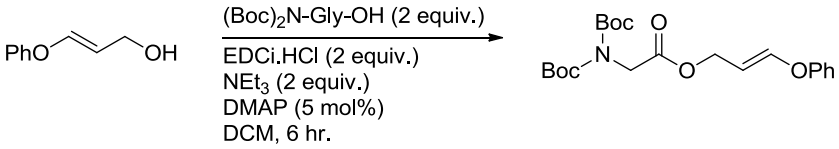
OCH_2CH=CHOAr), 6.73 (d, 1H, *J* = 12.7 Hz, OCH_2CH=C*H*OAr), 7.23 – 7.36 (m, 3H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0, 47.4, 63.2, 66.1, 83.0, 98.4, 128.4, 130.6, 131.7, 136.9, 151.9, 152.3, 169.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{22}H_{29}NO_7Cl_2Na$ 512.1190, found 512.1194 $(M+Na)^+$.

(*S*,*E*)-3-(1-Phenylethoxy)allyl 2-(bis(tert-butoxycarbonyl)amino)acetate (359)



EDCi.HCl (0.56 g, 2.90 mmol), triethylamine (0.40 mL, 2.90 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.80 g, 2.90 mmol), catalytic DMAP and *(S,E)*-3-(1-phenylethoxy)prop-2-enol **349** (0.26 g, 1.45 mmol) were combined according to general procedure 3 to afford the title compound as a yellow oil (0.31 g, 49%). $[\alpha]_D^{20}$ = -60° (*c* 1 DCM); FTIR (film/cm^{-1}) υ_{max}: 3002.5, 2999.3, 2985.2, 1754.6, 1734.2, 1698.2, 1651.7; ^{1}H NMR (500 MHz, d_6-acetone) δ: 1.02 – 1.13 (m, 3H, OCH(C*H*$_3$)Ph), 1.37 (s, 18H, (C*H*$_3$)$_3$COCON), 4.14 (s, 2H, NC*H*$_2$CO$_2$), 4.38 (d, 2H, *J* = 7.9 Hz, OC*H*$_2$CH=CHO), 4.85 – 4.97 (m, 2H, OCH_2CH=CHO & OC*H*(CH$_3$)Ph), 6.53 (d, 1H, *J* = 12.7 Hz, OCH_2CH=C*H*O), 7.08 – 7.34 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, d_6-acetone) δ: 23.9, 28.4, 46.4, 58.8, 77.7, 82.6, 106.6, 125.7, 127.9, 128.9, 143.4, 147.4, 152.7, 169.5; HRMS (ESI, +ve) *m/z*: calcd. for $C_{23}H_{33}NO_7Na$ 458.2155, found 458.2140 $(M+Na)^+$.

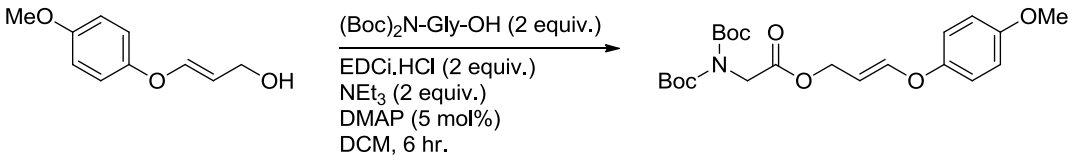
(*E*)-3-Phenoxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (360)



EDCi.HCl (0.58 g, 3.03 mmol), triethylamine (0.42 mL, 3.03 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.84 g, 3.03 mmol), catalytic DMAP and (*E*)-3-phenoxyprop-2-enol **255** (0.23 g, 1.51 mmol) were combined according to general procedure 3 to afford the title compound as a yellow oil (0.62 g, 95%). FTIR (film/cm^{-1}) υ_{max}: 2980.1, 2936.0, 1755.7, 1735.9, 1697.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.51 (s, 18H, (C*H*$_3$)$_3$COCON), 4.35 (s, 2H, NC*H*$_2$CO$_2$), 4.67 (d, 2H, *J* = 7.9 Hz, OC*H*$_2$CH=CHOPh), 5.45 (dt, 1H, *J* = 12.4, 7.9 Hz, OCH_2CH=CHOPh), 6.82 (d, 1H, *J* = 12.4 Hz, OCH_2CH=C*H*OPh), 7.01 (d, 2H, *J* = 8.3 Hz, Ar-*H* Ph), 7.11 (t, 1H, *J* = 8.3 Hz,

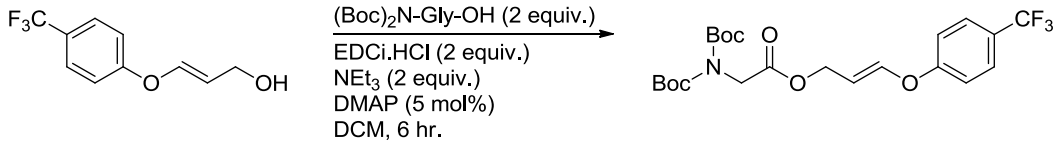
Ar-*H* Ph), 7.34 (t, 2H, *J* = 8.3 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4, 47.6, 62.6, 83.0, 105.1, 117.2, 123.6, 130.0, 148.5, 152.0, 156.8, 169.3; HRMS (ESI, +ve) *m/z*: calcd. for $C_{21}H_{29}NO_7Na$ 430.1842, found 430.1827 $(M+Na)^+$.

(*E*)-3-(4-Methoxyphenyloxy)allyl 2-bis(*tert*(butoxycarbonyl)amino)acetate (361)



EDCi.HCl (0.41 g, 2.14 mmol), triethylamine (0.30 mL, 2.14 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.59 g, 2.14 mmol), catalytic DMAP and (*E*)-3-(4-methoxyphenyloxy)prop-2-enol **256** (0.20 g, 1.07 mmol) were combined according to general procedure 3 to afford the title compound as a yellow oil (0.41 g, 79%). FTIR (film/cm^{-1}) υ_{max}: 2979.9, 2940.1, 1796.2, 1755.6, 1735.3, 1697.3, 1673.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.47 (s, 18H, $(CH_3)_3OCON$), 3.75 (s, 3H, CH_3OPh), 4.30 (s, 2H, NCH_2CO_2), 4.60 (d, 2H, *J* = 7.7 Hz, $OCH_2CH{=}CHO$), 5.29 (dt, 1H, *J* = 12.2, 7.7 Hz, $OCH_2CH{=}CHO$), 6.72 (d, 1H, *J* = 12.2 Hz, $OCH_2CH{=}CHO$), 6.82 (app. dt, 2H, *J* = 8.9, 2.9 Hz, Ar-*H* Ph), 6.90 (app. dt, 2H, *J* = 8.9, 2.9 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.9, 47.4, 55.6, 62.4, 83.1, 103.7, 114.7, 118.6, 150.0, 150.3, 151.8, 155.9, 169.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{22}H_{31}NO_7Na$ 460.1947, found 460.1916 $(M+Na)^+$.

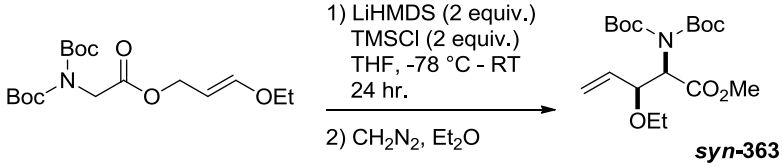
(*E*)-3-(4-Trifluoromethylphenoxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (362)



EDCi.HCl (0.33 g, 1.72 mmol), triethylamine (0.22 mL, 1.72 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.47 g, 1.72 mmol), catalytic DMAP and (*E*)-3-bezyloxyprop-2-enol **258** (0.19 g, 0.86 mmol) were combined according to general procedure 3 to afford the title compound as a colourless oil (0.40 g, 96%). FTIR (film/cm^{-1}) υ_{max}: 3013.2, 2937.1, 1795.5, 1756.0, 1735.2, 1698.6, 1612.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.51 (s, 18H, $(CH_3)_3COCON$), 4.36 (s, 2H, NCH_2CO_2), 4.69 (dd, 2H, *J* = 7.6, 1.0 Hz, $OCH_2CH{=}CHO$), 5.55 (dt, 1H, *J* = 12.2, 7.6 Hz, $OCH_2CH{=}CHO$), 6.82 (dt, 1H , *J* = 12.2, 1.0 Hz, $OCH_2CH{=}CHO$), 7.09 (app. d, 2H, *J* = 8.6 Hz, Ar-*H* Ph),

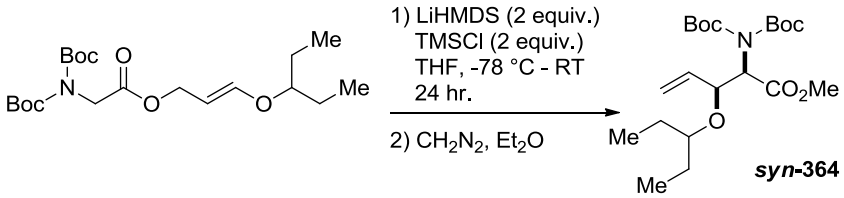
7.60 (app. d, 2H, *J* = 8.6 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0, 47.3, 61.7, 83.2, 107.3, 116.9, 125.4, 125.7, 127.2 (q, *J* = 3.8 Hz), 146.9, 152.0, 158.9, 169.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{22}H_{28}F_3NO_7Na$ 498.1716, found 498.1719 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-ethoxypent-4-enoate (363)



(*E*)-3-Ethoxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **350** (0.10 g, 0.27 mmol), TMSCl (0.07 mL, 0.53 mmol) and LiHMDS (0.53 mL, 0.53 mmol) were combined according to general procedure7. Treatment with diazomethane and purification by flash chromatography (10:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.07 g, 56% as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 2980.4, 2937.3, 1794.1, 1748.2, 1698.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.14 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 1.52 (s, 18H, $(CH_3)_3COCON$), 3.30 (dq, 1H, *J* = 9.2, 7.0 Hz, OCH_2CH_3), 3.59 (dq, 1H, *J* = 9.2, 7.0 Hz, OCH_2CH_3), 3.71 (s, 3H, CO_2CH_3), 4.32 (dd, 1H, *J* = 9.0 2.4 Hz, H_2C=CHC*H*O), 4.86 (d, 1H, *J* = 9.0 Hz, NC*H*CO_2), 5.28 (dq, 1H, *J* = 10.4, 1.0 Hz, H_2C=CHCHO), 5.42 (dq, 1H, *J* = 17.2, 1.0 Hz, H_2C=CHCHO), 5.96 (ddd, 1H, *J* = 17.2, 10.4, 2.4 Hz, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.2, 28.0, 47.2, 51.9, 61.6, 64.6, 82.7, 117.7, 137.2, 152.24, 169.5; HRMS (ESI, +ve) *m/z*: calcd. for $C_{18}H_{31}NO_7Na$ 396.1998, found 396.2001 $(M+Na)^+$.

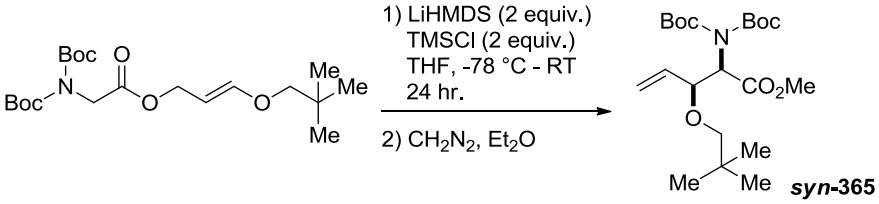
(±)-(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-(pentan-3-yloxy)pent-4-enoate (364)



(*E*)-3-(Pentan-3-yloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **351** (0.22 g, 0.55 mmol), TMSCl (0.14 mL, 1.10 mmol) and LiHMDS (1.10 mL, 1.10 mmol) were combined according to general procedure 7. Treatment with diazomethane and purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.10 g, 45% as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 2980.0, 2937.7, 2879.8, 1797.7, 1751.0, 1698.6; ^{1}H NMR (500 MHz, d_6-acetone)

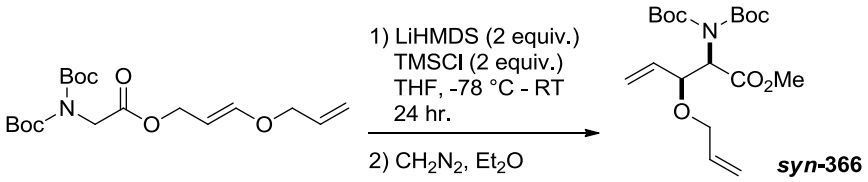
δ: 0.84 (t, 6H, *J* = 7.6 Hz, ((CH_3CH_2)$_2$CHO), 1.48 – 1.51 (m, 22H, (CH_3)$_3$COCON & ((CH_3CH_2)$_2$CHO), 3.31 (quin, 1H, *J* = 5.9 Hz, (CH_3CH_2)$_2$C*H*O), 3.66 (s, 3H, CO_2CH_3), 4.45 (dd, 1H, *J* = 9.2, 2.3 Hz, H_2C=CHC*H*O), 4.84 (d, 1H, *J* = 9.2 Hz, NC*H*CO_2), 5.25 (dd, 1H, *J* = 10.5, 1.7 Hz, *H*$_2$C=CHCHO), 5.39 (d, 1H, *J* = 17.1 Hz, *H*$_2$C=CHCHO), 5.94 (ddd, 1H, *J* = 17.1, 10.5, 9.2 Hz, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, d_6-acetone) δ: 8.0, 9.2, 24.2, 25.7, 27.3, 51.2, 61.8, 75.0, 78.2, 82.0, 117.3, 138.5, 152.2, 168; HRMS (ESI, +ve) *m/z*: calcd. for $C_{21}H_{37}NO_7Na$ 416.2648, found 416.2625 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-isopropoxypent-4-enoate (365)



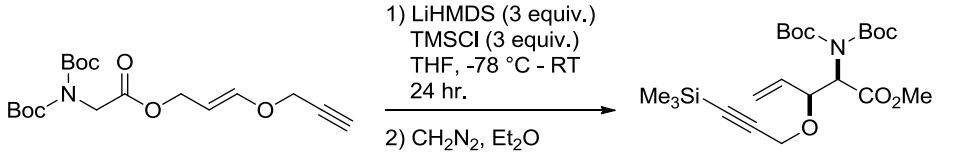
(*E*)-3-(Neopentyloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **353** (0.10 g, 0.25 mmol), TMSCl (0.06 mL, 0.49 mmol) and LiHMDS (0.49 mL, 0.49 mmol) were combined according to general procedure 7. Treatment with diazomethane and purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.08 g, 80% as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 2979.6, 2955.0, 1796.3, 1749.2, 1698.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (s, 9H, $OCH_2C(CH_3)_3$), 1.51 (s, 18H, (CH_3)$_3$COCON), 2.80 (d, 1H, *J* = 8.4 Hz, $OCH_2C(CH_3)_3$), 3.23 (d, 1H, *J* = 8.4 Hz, $OCH_2C(CH_3)_3$), 3.70 (s, 3H, CO_2CH_3), 4.28 (dd, 1H, *J* = 9.0, 2.4 Hz, H_2C=CHC*H*O) 4.94 (d, 1H, *J* = 9.0 Hz, NC*H*CO_2), 5.30 (dd, 1H, *J* = 10.3, 1.9 Hz, *H*$_2$C=CHCHO), 5.43 (dt, 1H, *J* = 17.4, 1.9 Hz, *H*$_2$C=CHCHO), 5.90 (ddd, 1H, *J* = 17.4, 10.3, 8.4 Hz, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.8, 28.1, 32.0, 51.9, 61.7, 77.3, 79.4, 82.8, 118.1, 137.6, 152.0, 169; HRMS (ESI, +ve) *m/z*: calcd. for $C_{21}H_{38}NO_7$ 416.2648, found 416.2620 $(M+H)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-allyloxypent-4-enoate (366)



(*E*)-3-Allyloxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **354** (0.12 g, 0.21 mmol), TMSCl (0.05 mL, 0.41 mmol) and LiHMDS (0.41 mL, 0.41 mmol) were combined according to general procedure 7. Treatment with diazomethane and purification by flash chromatography (10:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.08 g, 65% as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 2981.7, 2935.6, 1747.9, 1698.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.51 (s, 18H, $(CH_3)_3COCON$), 3.70 (s, 3H, CO_2CH_3), 3.81 (ddt, 1H *J* = 12.9, 5.7, 1.6 Hz, H_2C=CHCH_2O), 4.07 (ddt, 1H, *J* = 12.9, 5.7, 1.6 Hz, H_2C=CHCH_2O), 4.36 – 4.40 (m, 1H, H_2C=CHC*H*O), 4.91 (d, 1H, *J* = 8.9 Hz, NC*H*CO_2), 5.12 (dq, 1H, *J* = 10.5, 1.6 Hz, H_2C=CHCHO), 5.24 (dq, 1H, *J* = 17.2, 1.6 Hz, H_2C=CHCHO), 5.32 (dq, 1H, *J* = 10.5, 1.0 Hz, H_2C=CHCH_2), 5.43 (dq, 1H, *J* = 17.2, 1.0 Hz, H_2C=CHCH), 5.80 – 5.88 (m, 1H, H_2C=C*H*CH_2O), 5.94 (ddd, 1H, *J* = 17.2, 10.5, 6.8 Hz, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ:28.0, 51.9, 61.5, 69.6, 74.9, 82.9, 116.4, 118.4, 134.7, 136.7, 152.2, 169.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{19}H_{31}NO_7Na$ 408.1998, found 408.1976 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-(3-(trimethylsilyl)prop-2-ynyloxy)pent-4-enoate (367)

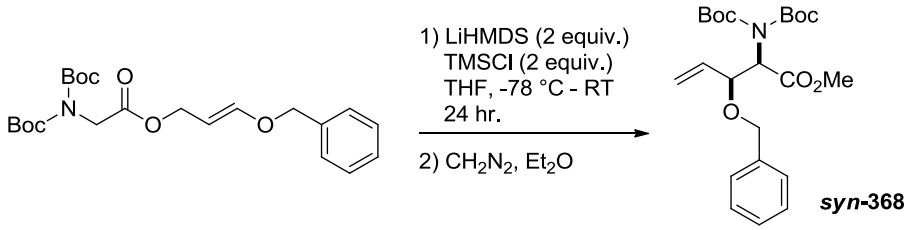


***syn*-367**

(*E*)-3-(Prop-2-yn-1-yloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **355** (0.10 g, 0.30 mmol, 1 equiv.), TMSCl (0.10 mL, 0.89 mmol, 3 equiv.) and LiHMDS (0.89 mL, 0.89 mmol, 3 equiv.) were combined according to general procedure 7. Treatment with diazomethane and purification by flash chromatography (10:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.10 g, 71% as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 2979.7, 2867.7, 2182.2, 1794.0, 1749.6, 1700.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.16 (s, 9H, $Si(CH_3)_3$), 1.52 (s, 18H, $(CH_3)_3COCON$), 3.70 (s, 3H, CO_2CH_3), 4.05 (d, 1H, *J* = 15.6 Hz, OCH_2C≡CSi), 4.17 (d, 1H, *J* = 15.6 Hz, OCH_2C≡CSi), 4.51 (app. t, 1H, *J* = 8.0 Hz, H_2C=CHC*H*O), 4.93 (d, 1H, *J* = 8.0 Hz, NC*H*CO_2), 5.36 (d, 1H, *J* = 10.6 Hz, H_2C=CHCHO), 5.48 (d, 1H, *J* = 17.2 Hz, H_2C=CHCHO), 5.86 (ddd, 1H, *J* = 17.2, 10.6, 8.0 Hz, H_2C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -0.2, 28.0, 51.9, 56.6, 61.2, 76.5, 82.9, 90.9, 101.6, 119.8, 135.7, 152.1,

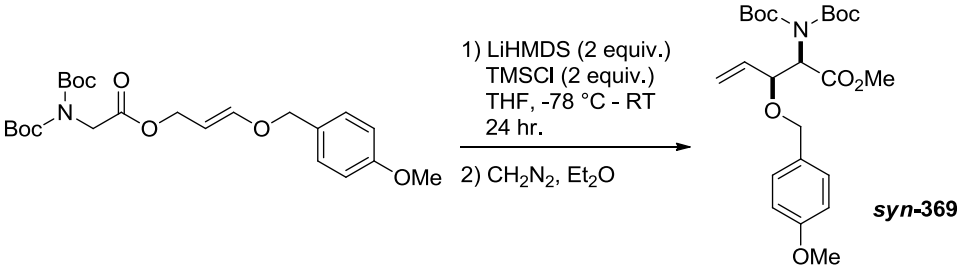
169.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{22}H_{37}NO_7SiNa$ 478.2237, found 478.2222 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-(benzyloxy) pent-4-enoate (368)



(*E*)-3-Benzyloxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **356** (0.09 g, 0.22 mmol), TMSCl (0.05 mL, 0.43 mmol) and LiHMDS (0.43 mL, 0.43 mmol) were combined according to general procedure 7. Treatment with diazomethane and purification by flash chromatography (10:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.05 g, 55% as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 2980.7, 2890.6, 1750.9, 1700.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (s, 18H, $(CH_3)_3COCON$), 3.71 (s, 3H, CO_2CH_3), 4.33 (d, 1H, *J* = 11.6 Hz, OCH_2Ph), 4.47 (dd, 1H, *J* = 9.1, 2.1 Hz, H_2C=CHC*H*O), 4.61 (d, 1H, *J* = 11.6 Hz, OCH_2Ph), 4.99 (d, 1H, *J* = 9.1 Hz, $NCHCO_2$), 5.38 (dd, 1H, *J* = 10.4, 1.4 Hz, H_2C=CHCHO), 5.49 (dd, 1H, *J* = 17.3, 1.4 Hz, H_2C=CHCHO), 5.89 (ddd, 1H, *J* = 17.3, 10.4, 9.1 Hz, H_2C=C*H*CHO), 7.23 – 7.39 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.9, 52.0, 61.6, 70.5, 77.2, 82.9, 118.9, 127.3, 127.7, 128.1, 136.6, 138.3, 152.3, 169.3; HRMS (ESI, +ve) *m/z*: calcd. for $C_{23}H_{33}NO_7Na$ 458.2155, found 458.2161 $(M+Na)^+$.

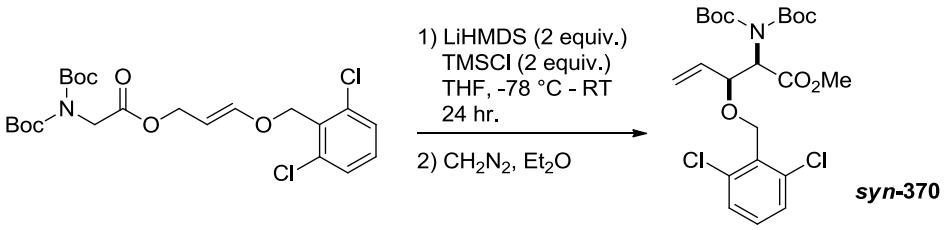
(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-(4-methoxybenzyloxy)pent-4-enoate (369)



(*E*)-3-(4-Methoxybenzyloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **357** (0.14 g, 0.31 mmol), TMSCl (0.08 mL, 0.62 mmol) and LiHMDS (0.62 mL, 0.62 mmol) were combined according to general procedure 7. Treatment with diazomethane and

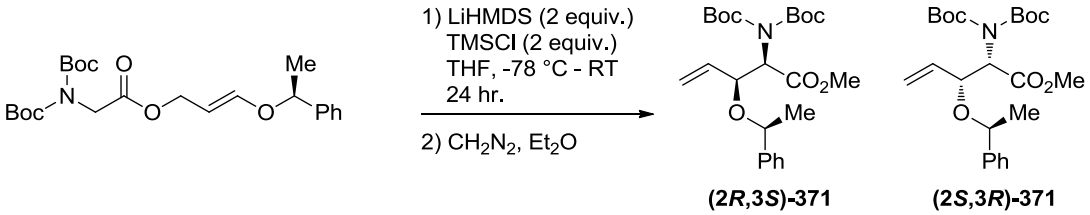
purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.06 g, 40% as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 3010.5, 2955.0, 1794.7, 1751.3, 1697.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (s, 18H, $(CH_3)_3COCON$), 3.70 (s, 3H, OCH_2PhOCH_3), 3.80 (s, 3H, CO_2CH_3), 4.26 (d, 1H, *J* = 9.7, OCH_2Ar), 4.44 (dd, 1H, *J* = 8.5, 6.9 Hz, H_2C=CHC*H*O), 4.53 (d, 1H, *J* = 9.7 Hz, OCH_2Ar), 4.95 (d, 1H, *J* = 8.5 Hz, $NCHCO_2$), 5.37 (dd, 1H, *J* = 10.4, 1.1 Hz, H_2C=CHCHO), 5.47 (dd, 1H, *J* = 17.7, 1.1 Hz, H_2C=CHCHO), 5.98 (ddd, 1H, *J* = 17.7, 10.4, 6.9 Hz, H_2C=C*H*CHO), 6.84 (d, 2H, *J* = 8.4 Hz, Ar-*H* Ph), 7.23 (d, 2H, *J* = 8.4 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.9, 51.9, 55.2, 61.7, 65.8, 70.2, 82.9, 113.6, 118.7, 129.3, 130.2, 130.5, 136.7, 152.2, 159.0, 169.3; HRMS (ESI, +ve) *m/z*: calcd. for $C_{24}H_{35}NO_7Na$ 488.2260, found 488.2243 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-(2,6-dichlorobenzyloxy) pent-4-enoate (370)



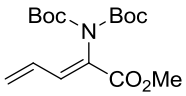
(*E*)-2,6-Dichlorobenzyloxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **358** (0.07 g, 0.15 mmol), TMSCl (0.04 mL, 0.30 mmol) and LiHMDS (0.30 mL, 0.30 mmol) were combined according to general procedure 7. Treatment with diazomethane and purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.06 g, 78% as a single diastereomer). FTIR (film/cm^{-1}) υ_{max}: 2979.9, 2933.7, 1796.6, 1749.3, 1697.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (s, 18H, $(CH_3)_3COCON$), 3.70 (s, 3H, CO_2CH_3), 4.51 – 4.54 (m, 2H, $NCHCO_2$ & H_2C=CHC*H*O), 4.89 (dd, 2H, *J* = 36.6, 9.6 Hz, OCH_2Ar), 5.42 (dd, 1H, *J* = 10.7, 0.6 Hz, H_2C=CHCHO), 5.61 (dq, 1H, *J* = 17.4, 0.6 Hz, H_2C=CHCHO), 6.05 (ddd, 1H, *J* = 17.4, 10.7, 6.9 Hz, H_2C=C*H*CHO), 7.15 (dd, 1H, *J* = 8.7, 0.9 Hz, Ar-*H* Ph), 7.28 (d, 2H, *J* = 8.7 Hz, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 51.9, 62.0, 65.3, 77.7, 82.6, 118.9, 128.1, 129.7, 133.7, 136.5, 137.1, 152.0, 169.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{23}H_{31}Cl_2NO_7Na$ 504.1556, found 504.1562 $(M+Na)^+$.

(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-((*S*)-1-phenylethoxy)pent-4-enoate (371)



(*S*,*E*)-3-(1-Phenylethoxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **359** (0.24 g, 0.54 mmol), TMSCl (0.14 mL, 1.08 mmol) and LiHMDS (1.08 mL, 1.08 mmol) were combined according to general procedure 7. Treatment with diazomethane and purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.10 g, 42% as a 2.25:1 mixture of diastereomers). FTIR (film/cm^{-1}) υ_{max}: 2982.7, 1789.2, 1745.6, 1696.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ **(2*R*,3*S*)-371** : 1.38 (d, 3H, *J* = 6.3 Hz, OCH(C*H*$_3$)Ph), 1.52 (s, 18H, (C*H*$_3$)$_3$COCON), 3.71 (s, 3H, CO_2CH_3), 4.35 (d, 1H, *J* = 6.2 Hz, NC*H*CO_2), 4.56 (q, 1H, *J* = 6.3 Hz, OC*H*(CH$_3$)Ph), 4.92 - 4.95 (m, 1H, H_2C=CHC*H*O), 5.16 – 5.34 (m ,2H, *H*$_2$C=CHCHO), 5.90 (ddd, 1H, *J* = 17.1, 10.8, 6.7 Hz, H_2C=C*H*CHO), 7.21 -7.36 (m, 5H, Ar-*H* Ph); δ **(2*S*,3*R*)-371**: 1.35 (d, 1H, *J* = 6.3 Hz, OCH(C*H*$_3$)Ph), 1.52 (s, 18H, (C*H*$_3$)$_3$COCON), 3.64 (s, 3H, CO_2CH_3),4.34 (d, 1H, *J* = 6.2 Hz, NC*H*CO_2), 4.56 (q, 1H, *J* = 6.3 Hz, OC*H*(CH$_3$)Ph), 4.92 - 4.95 (m, 1H, H_2C=CHC*H*O), 5.37 - 5.42 (m ,2H, *H*$_2$C=CHCHO), 5.97 (ddd, 1H, *J* = 13.8, 10.0, 6.7 Hz, H_2C=C*H*CHO), 7.21 -7.36 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ **(2*R*,3*S*)-371**: 22.3, 28.0, 51.9, 61.8, 73.2, 75.2, 83.0, 118.0, 126.2, 126.7, 128.0, 128.5, 137.4, 152.3, 169.4; δ **(2*S*,3*R*)-371**: 22.1, 27.9, 51.7, 62.2,73.3, 75.6, 82.8, 118.0, 126.1, 126.8, 128.1, 128.4, 137.5, 151.8, 168.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{24}H_{35}NO_7Na$, 472.2311 found 472.2293 $(M+Na)^+$.

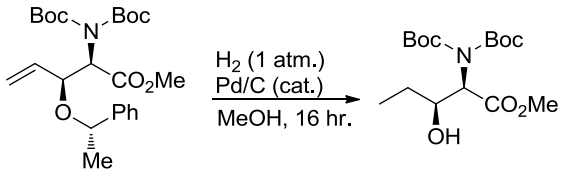
(*Z*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)penta-2,4-dienoate (372)



FTIR (film/cm^{-1}) υ_{max}: 2914.3, 2851.5, 1796.6, 1727.8, 1644.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (s, 18H, (C*H*$_3$)$_3$COCON), 3.81 (s, 3H, CO_2CH_3), 5.58 (d, 1H, *J* = 10.8 Hz, *H*$_2$C=CHCH=C), 5.71 (d, 1H, *J* = 17.3 Hz, *H*$_2$C=CHCH=C), 6.50 (dt, 1H, *J* = 17.3, 10.8 Hz, H_2C=C*H*CH=C), 7.17 (d, 1H, *J* = 10.8 Hz, H_2C=CHC*H*=C); ^{13}C NMR (125

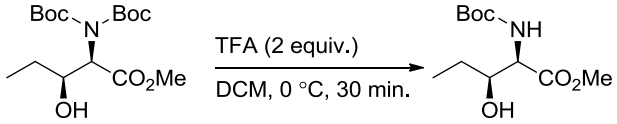
MHz, $CDCl_3$) δ: 27.8, 52.3, 83.0, 126.9, 128.0, 130.2, 136.8, 150.4, 165.0; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{25}NO_6Na$ 350.1580, found 350.1578 $(M+Na)^+$.

(2*R*,3*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-hydroxypent-4-enoate (373)



To a stirred solution of (2*R*,3*S*)-methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-((*S*)-1-phenylethoxy)pent-4-enoate **371** (0.08 g, 0.17 mmol) in methanol (20 mL) was added catalytic palladium on carbon (0.02 g) and stirred under an atmosphere of hydrogen for 16 hours. The solution was filtered through celite and washed with another 20 mL of methanol, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (0.04 g, 73%). FTIR (film/cm^{-1}) υ_{max}: 3428.0, 2980.0, 1737.2, 1693.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00 (t, 3H, *J* = 7.6 Hz, C*H*$_3$CH$_2$), 1.49 – 1.52 (m, 2H, CH$_3$C*H*$_2$), 1.53 (s, 18H, (C*H*$_3$)$_3$COCON), 3.78 (s, 3H, CO$_2$C*H*$_3$), 3.96 (d, 1H, *J* = 9.0 Hz, NC*H*CO$_2$), 4.11 – 4.17 (m, 1H, CH$_3$CH$_2$C*H*OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.2, 27.5, 27.9, 52.4, 62.4, 72.5, 83.6, 153.4, 169.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{29}NO_7Na$ 370.3937, found 370.3940 $(M+Na)^+$.

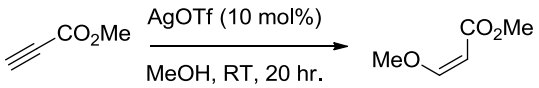
(2*R*,3*S*)-Methyl 2-((tert-butoxycarbonyl)amino)-3-hydroxypentanoate (374)



To a stirred solution of (2*R*,3*S*)-methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-hydroxypent-4-enoate **373** (0.07 g, 0.19 mmol, 1 equiv.) in DCM (5 mL) was added TFA (0.03 mL, 0.38 mmol, 2 equiv.) at 0 °C. The mixture was stirred for 30 minutes before concentrating *in vacuo*. The residue was taken up in saturated sodium bicarbonate solution (10 mL) and extracted with EtOAc (4 × 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification was achieved by flash chromatography (2:1 Pet/EtOAc) to afford the title compound as a colourless oil. (0.04 g, 78%). $[\alpha]_D^{20}$ = +3.2° (*c* 0.85 EtOH abs.); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.94 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$), 1.42 (s, 9H, (C*H*$_3$)$_3$COCON), 1.51 – 1.55 (m, 2H, CH$_3$C*H*$_2$), 3.71 (s, 3H, CO$_2$C*H*$_3$), 3.97 – 3.99 (m, 1H, CH$_3$CH$_2$C*H*O), 4.19 (br, 1H, O*H*), 4.23 (d, 1H, *J* =9.0 Hz, NC*H*CO$_2$), 5.72 (br, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.0, 27.8,

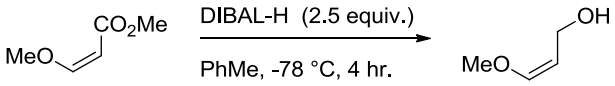
28.3, 52.2, 58.3, 73.7, 80.1, 155.5, 173.7. All analytical data is in accordance with reported literature values.[140]

(*Z*)-Methyl 3-methoxyacrylate ((*Z*)-223)



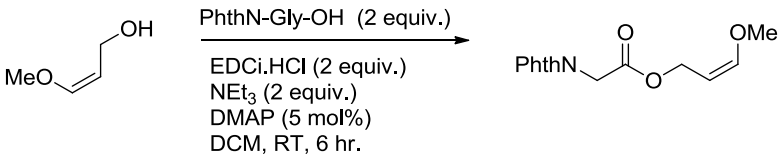
To a stirred solution of silver (I) trifluoromethanesulfonate (0.29 g, 1.12 mmol, 0.1 equiv.) in methanol (15 mL) was added methyl propiolate **232** (0.95 g, 11.2 mmol, 1 equiv.). The solution was stirred at room temperature for 20 hours and concentrated *in vacuo*. The solution was taken up in chloroform, filtered through celite and concentrated to afford the title compound as a pale brown oil (1.10 g, 71%). FTIR (film/cm^{-1}) υ_{max}: 2990.0, 2950.5, 2877.1, 2833.7, 1709.4, 1646.2, 1626.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.65 (s, 3H, CO_2CH_3), 3.84 (s, 3H, CH_3O), 4.82 (d, 1H, *J* = 7.1 Hz, $CH_3OCH{=}CHCO_2CH_3$), 6.43 (d, 1H, *J* = 7.1 Hz, $CH_3OCH{=}CHCO_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 50.8, 62.5, 95.9, 160.1, 165.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_5H_8O_3Na$ 139.0371, found 139.0378 $(M+Na)^+$.

(*Z*)-3-(Methoxy)prop-2-enol ((*Z*)-224)



(*Z*)-Methyl 3-(methoxy)acrylate **(*Z*)-223** (0.51 g, 4.39 mmol) was reduced according to general procedure 5 to afford the title compound as a colourless oil (0.13 g, 33%). FTIR (film/cm^{-1}) υ_{max}: 3337.8, 3046.0, 2936.2, 2859.6, 1662.9; ^{1}H NMR (300 MHz, d_6-acetone) δ: 1.85 (br, 1H, CH_2OH), 3.63 (s, 3H, CH_3O), 4.16 (dd, 2H, *J* = 6.9, 1.1 Hz, $CH_3OCH{=}CHCH_2OH$), 4.64 (q, 1H, *J* = 6.9 Hz, $CH_3OCH{=}CHCH_2OH$), 6.02 (dt, 1H, *J* = 6.9, 1.2 Hz, $CH_3OCH{=}CHCH_2OH$); ^{13}C NMR (75 MHz, d_6-acetone) δ: 56.9, 60.6, 106.3, 149.2.

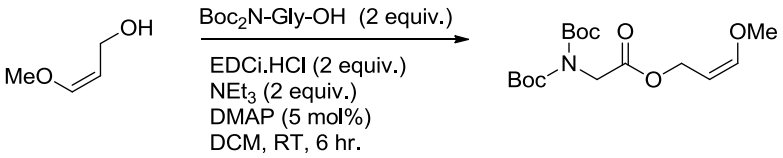
(*Z*)-3-Methoxyallyl 2-(1,3-dioxoisoindolin-2-yl)acetate ((*Z*)-229)



EDCi.HCl (0.54 g, 2.95 mmol), triethylamine (0.4 mL, 2.95 mmol), phthaloyl glycine **228** (0.58 g, 2.95 mmol), catalytic DMAP and (*Z*)-3-(methoxy)prop-2-enol **(*Z*)-224**

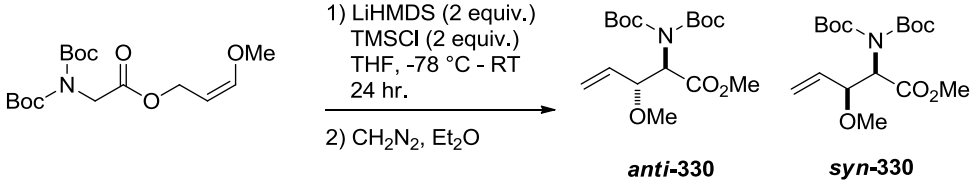
(0.13 g, 1.48 mmol) were combined according to general procedure 3, to afford the title compound as a white solid (0.24 g, 60%). MP: 55 - 58 °C; FTIR (film/cm^{-1}) υ_{max}: 2993.7, 2880.3, 1757.6, 1736.1, 1718.0, 1671.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.58 (s, 3H, OCH_3), 4.43 (s, 2H, NCH_2CO$_2$), 4.61 (d, 2H, *J* = 8.2 Hz, OCH_2CH=CHO), 4.92 (dt, 1H, *J* = 12.6, 8.2 Hz, OCH$_2$C*H*=CHO), 6.65 (d, 1H, *J* = 12.6 Hz, OCH$_2$CH=C*H*O), 7.77 – 7.73 (m, 2H, Ar-*H* Phth), 7.91 – 7.88 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.0, 56.2, 64.2, 96.3, 123.6, 132.1, 134.2, 154.0, 167.3, 167.5; HRMS (ESI, +ve) *m/z* calcd. for $C_{14}H_{13}NO_5Na$ 298.0692, found 298.0675. (M+Na)$^+$.

(*Z*)-3-Methoxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate ((*Z*)-314)



EDCi.HCl (1.06 g, 5.45 mmol), triethylamine (0.76 mL, 5.45 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (1.52 g, 5.45 mmol), catalytic DMAP and (*Z*)-3-methoxyprop-2-enol **(*Z*)-224** (0.24 g, 2.72 mmol) were combined according to general procedure 3 to afford a yellow oil. Purification by flash chromatography (Al_2O, 15:1 Pet/EtOAc) afforded the title compound as colourless oil (0.28 g, 30%). FTIR (film/cm^{-1}) υ_{max}: 2979.6, 2937.6, 1799.3, 1756.9, 1736.0, 1697.7, 1666.7; ^{1}H NMR (500 MHz, d_6-acetone) δ: 1.48 (s, 18H, (CH_3)$_3$COCON), 3.65 (s, 3H, OCH_3), 4.28 (s, 2H, NCH_2CO$_2$), 4.54 – 4.58 (m, 1H, OCH$_2$C*H*=CHOCH$_3$), 4.67 (dd, 2H, *J* = 7.8, 0.9 Hz, OCH_2CH=CHOCH$_3$), 6.21 (dt, 1H, *J* = 6.3, 1.1 Hz, OCH$_2$CH=C*H*OCH$_3$); ^{13}C NMR (125 MHz, d_6-acetone) δ: 32.4, 52.2, 63.3, 64.6, 87.3, 104.6, 156.0, 157.0, 174.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{27}NO_7Na$ 368.1685, found 368.1684 (M+Na)$^+$.

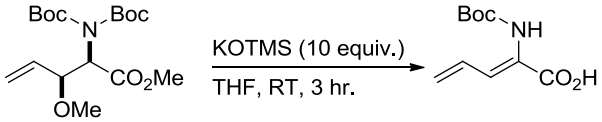
((±)-(2*R*,3*R*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-methoxypent-4-enoate (*anti*-330)



(*Z*)-3-Methoxyallyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **(*Z*)-314** (0.10 g, 0.29 mmol), TMSCl (0.07 mL, 0.58 mmol) and LiHMDS (0.58 mL, 0.58 mmol) were combined according to general procedure 7. Treatment with diazomethane and

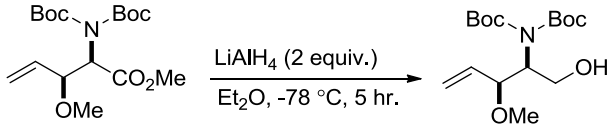
purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil (0.06 g, 55%, dr 1.5:1). A small fraction of the major *anti* product was isolated for identification. FTIR (film/cm^{-1}) υ_{max}: 2983.1, 2932.2, 1788.9, 1745.9, 1695.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ ***anti*-330**: 1.49 (s, 18H, $(CH_3)_3COCON$), 3.37 (s, 3H, $CHOCH_3$), 3.76 (s, 3H, CO_2CH_3), 4.28 (t, 1H, *J* = 8.2 Hz, H_2C=CHC*H*OCH_3), 4.86 (d, 1H, *J* = 8.2 Hz, $NCHCO_2$), 5.25 – 5.32 (m, 2H, H_2C=CHCHOCH_3), 5.61 (ddd, 1H, *J* = 17.9, 9.5, 8.2 Hz, H_2C=C*H*$CHOCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ ***anti*-330**: 28.0, 52.2, 56.5, 60.5, 82.1, 83.3, 120.1, 133.8, 151.6, 170.0; HRMS (ESI, +ve) *m/z*: calcd. for $C_{17}H_{30}NO_7$ 360.2022, found 360.2032 $(M+H)^+$.

(*Z*)-2-(*tert*-Butoxycarbonylamino)penta-2,4-dienoic acid (383)



To a stirred solution of (±)-(2*R*,3*S*)-methyl 2-(bis(*tert*butoxycarbonyl)amino)-3-methoxypent-4-enoate **330** (0.04 g, 0.11 mmol, 1 equiv.) in THF (2 mL) was added Potassium trimethylsilanolate (0.14 g, 1.11 mmol, 10 equiv.) and the mixture stirred at room temperature for 3 hours. Citric acid (0.5 M, 5 mL) was added and the biphasic mixture extracted with EtOAc (3 × 10 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification was achieved by flash chromatography (19:1 DCM/MeOH) to afford the title compound as a colourless oil (0.02 g, 100%). FTIR (film/cm^{-1}) υ_{max}: 3237.1, 2985.4, 1673.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.49 (s, 9H, $(CH_3)_3COCON$), 5.54 (d, 1H, *J* = 10.3 Hz, H_2C=CHCH=C), 5.65 (d, 1H, *J* = 17.8 Hz, H_2C=CHCH=C), 6.44 (br, 1H, N*H*), 6.63 (dt, 1H, *J* = 17.8, 10.3 Hz, H_2C=C*H*CH=C), 7.06 (d, 1H, *J* = 10.3 Hz, H_2C=CHC*H*=C); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.1, 81.4, 123.9, 125.5, 131.6, 133.1, 153.6, 169.7.

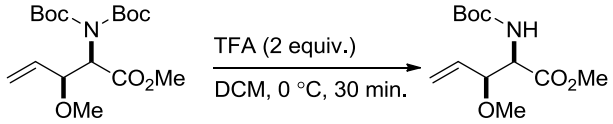
(2*S*,3*S*)-2-Bis(*tert*-butoxycarbonyl)amino-3-methoxypent-4-en-1-ol (384)



To a stirred solution of lithium aluminium hydride (0.01 g, 0.26 mmol, 2 equiv.) in ether (7 mL) at -78 °C was added a solution of (±)-(2*R*,3*S*)-methyl 2-(bis(*tert*butoxycarbonyl)amino)-3-methoxypent-4-enoate **330** (0.05 g, 0.13 mmol) in ether (3 mL). The mixture was stirred at -78 °C for 5 hours before quenching by the

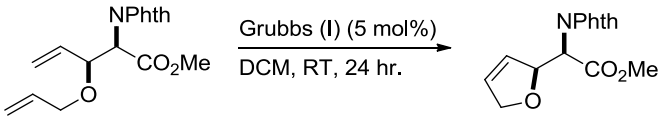
addition of EtOAc, then poured onto ice-cold saturated Rochelle salt solution (100 mL) followed by the addition of further EtOAc (100 mL). The biphasic mixture was vigorously stirred at 0 °C for 2 hours before separating and extracting with EtOAc (3 × 10 mL). The organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* Purification was achieved by flash chromatography (Pet/EtOAc 10:1) to afford the title compound as a colourless oil (0.03 g, 60%, 2:1 rotamers). FTIR (film/cm^{-1}) υ_{max}: 3338.7, 2967.3, 2928.0, 2882.8, 1705.4, 1596.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.49 & 1.56 (2s, 18H, (CH_3)$_3$COCON), 3.29 – 3.32 (m, 1H, NCHCH_2OH), 3.34 (s, 3H, CH_2CHCHOCH_3), 3.72 (t, 1H, *J* = 3.2 Hz, NCHCH_2OH), 3.94 (t, 1H, *J* = 7.9 Hz, CH_2CHC*H*OCH$_3$), 4.14 (dd, 1H, *J* = 7.9, 3.2 Hz, NC*H*CH_2OH), 4.67 (br, 1H, O*H*), 5.27 – 5.34 (m, 2H, CH_2CHCHO), 5.76 (ddd, 1H, *J* = 17.5, 9.9, 7.9 Hz, CH_2C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4 (×2), 56.9, 57.0, 57.3(×2), 79.4, 80.5, 119.5, 119.8, 127.5, 127.6, 133.9, 140.2, 135.8, 135.9, 152.8; 153.2; HRMS (ESI, +ve) *m/z*: calcd. for $C_{16}H_{30}NO_6Na$ 332.1995, found 332.2364 $(M+Na)^+$.

(±)-(2*R*,3*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-methoxypent-4-enoate (386)



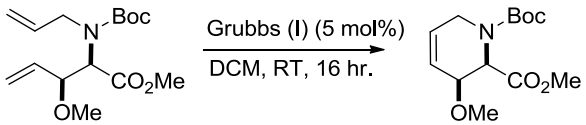
To a stirred solution of (±)-(2*R*,3*S*)-methyl 2-(bis(*tert*butoxycarbonyl)amino)-3-methoxypent-4-enoate **330** (0.07 g, 0.19 mmol, 1 equiv.) in DCM (5 mL) was added TFA (0.03 mL, 0.38 mmol, 2 equiv.) at 0 °C. The mixture was stirred for 30 minutes before concentrating *in vacuo*. The residue was taken up in saturated sodium bicarbonate solution (10 mL) and extracted with EtOAc (4 × 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification was achieved by flash chromatography (6:1 Pet/EtOAc) to afford the title compound as a colourless oil. (0.04 g, 78%) FTIR (film/cm^{-1}) υ_{max}: 3372.0, 2980.6, 2940.1, 1756.0, 1718.8, 1502.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (s, 9H, (CH_3)$_3$COCON), 3.26 (s, 3H, OCH_3), 3.78 (s, 3H, CO_2CH_3), 4.12 (d, 1H, *J* = 7.1 Hz, H_2C=CHC*H*OCH$_3$), 4.38 (dd, 1H, *J* = 7.1, 2.8 Hz, N*H*), 5.24 (d, 1H, *J* = 9.9 Hz, NC*H*CO_2), 5.34 – 5.39 (m, 2H, H_2C=CHCHOCH$_3$), 5.75 (ddd, 1H, *J* = 17.6, 9.9, 7.1 Hz, H_2C=C*H*CHOCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.3, 52.4, 56.9, 57.5, 79.9, 82.0, 119.6, 133.8, 155.9, 171.1; HRMS (ESI, +ve) *m/z*: calcd. for $C_{12}H_{21}NO_5Na$ 282.1317, found 282.1304 $(M+Na)^+$.

(±)-(*S*)-Methyl 2-((*R*)-2,5-dihydrofuran-2-yl)-2-(1,3-dioxoisoindolin-2-yl)acetate (387)



To a solution of (1*R*,2*R*)-2-(allyloxy)-1-(1,3-dioxoisoindolin-2-yl)but-3-enyl acetate **277** (0.14 g, 0.45 mmol, 1 equiv.) in DCM (5 mL) was added bis(tricyclohexylphosphine)benzylidine ruthenium(IV) chloride (0.02 g, 0.02 mmol, 0.05 equiv.) and stirred at room temperature for 24 hours. The mixture was passed through a pad of celite and concentrated *in vacuo*. Purification was achieved by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) to afford the title compound as a colourless oil (0.11 g, 87%, dr 10:1). FTIR (film/cm^{-1}) υ_{max}: 2955.0, 2907.9, 2855.2, 1777.4, 1746.9, 1716.3, 1614.0; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* δ: 3.77 (s, 3H, CO_2CH_3), 4.53 - 4.61 (m, 1H, NC*H*CO_2), 4.77 (d, 2H, *J* = 8.0 Hz, OCH_2CH=CH), 5.51 - 5.51 (m, 1H, OC*H*CH=CH), 6.02 - 6.04 (m, 1H, C*H*=CH), 6.18 - 6.20 (m, 1H, CH=C*H*), 7.72- 7.76 (m, 2H, Ar-*H* Phth), 7.86 - 7.89 (m, 2H, Ar-*H* Phth); *anti* δ: 3.80 (s, 3H, CO_2CH_3), 4.53 - 4.61 (m, 1H, NC*H*CO_2), 5.11 (d, 2H, *J* = 8.0 Hz, OCH_2CH=CH), 5.65 - 5.69 (m, 1H, OC*H*CH=CH), 6.02 - 6.04 (m, 1H, C*H*=CH), 6.18 - 6.20 (m, 1H, CH=C*H*), 7.72 - 7.76 (m, 2H, Ar-*H* Phth), 7.86 - 7.89 (m, 2H, Ar-*H* Phth); ^{13}C NMR (125 MHz, $CDCl_3$) *syn* δ: 52.7, 55.9, 75.2, 82.8, 123.6, 127.8, 128.9, 131.9, 134.1, 167.3, 168.0; *anti* δ: 52.6, 54.8, 75.7, 85.0, 123.6, 126.2, 128.8, 131.7, 134.2, 167.4, 167.9; HRMS (ESI, +ve) *m/z*: calcd. for $C_{15}H_{13}NO_5Na$ 310.0691, found 310.0673 $(M+Na)^+$.

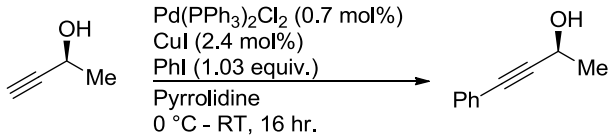
(2*R*,3*S*)-1-*tert*-Butyl 2-methyl 3-methoxy-2,3-dihydropyridine-1,2(6H)-dicarboxylate (388)



To a solution of (2*R*,3*S*)-methyl 2-(allyl(*tert*-butoxycarbonyl)amino)-3-methoxypent-4-enoate **328** (0.10 g, 0.33 mmol, 1 equiv.) in DCM (5 mL) was added bis(tricyclohexylphosphine)benzylidine ruthenium(IV) chloride (0.01 g, 0.02 mmol, 0.05 equiv.) and stirred at room temperature for 16 hours. The mixture was passed through a pad of celite and concentrated *in vacuo*. Purification was achieved by flash chromatography (6:1 Pet/EtOAc + 1% NEt_3) to afford the title compound as a

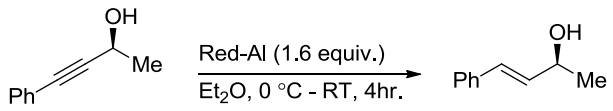
colourless oil (0.06 g, 67%, dr 2:1). FTIR (film/cm^{-1}) υ_{max}: 2954.3, 2907.9, 2855.2, 1781.2, 1715.3, 1614.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.48 (s, 9H, $(CH_3)_3COCON$), 3.53 (s, 3H, OCH_3), 3.71 (s, 3H, CO_2CH_3), 3.90 – 4.12 (m, 3H, NCH_2CH & $HC{=}CHCHOCH_3$), 5.26 – 5.40 (br m, 1H, $NCHCO_2$), 5.64 – 5.84 (br m, 2H, $NCH_2CH{=}CH$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.3, 42.8, 51.8, 57.4, 74.3, 80.9, 124.8, 128.6, 134.0, 155.2, 170.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{13}H_{21}NO_5Na$ 294.1317, found 294.1323 $(M+Na)^+$.

(*S*)-4-Phenylbut-3-yn-2-ol (432)



To a 100 mL Schlenk flask was added copper(I) iodide (0.6 g, 3.0 mmol, 0.02 equiv.) and bis(triphneylphosphine)palladium(II) chloride (0.1 g, 0.2 mmol, 0.01 equiv.). The flask was evacuated and flushed with nitrogen several times. Freshly distilled pyrrolidine (40 mL) was added followed by iodobenzene (3.4 mL, 31.0 mmol, 1.03 equiv.). The solution was cooled to 0 °C and (*S*)-butyn-2-ol **(*S*)-189** (2.3 mL, 30.0 mmol, 1.0 equiv.) was added dropwise. The ice bath was removed and the reaction mixture stirred at room temperature for 16 hours. The reaction was quenched by the addition of sat. NH_4Cl solution. The aqueous was extracted with DCM (3 x 50 mL), dried over MgSO4, filtered and concentrated *in vacuo*. Purification was achieved by flash chromatography (DCM) to afford the title compound as a yellow oil (4.4 g, 100%). $[\alpha]_D^{20}$ -29° (*c* 1, DCM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.57 (d, 3H, *J* = 6.7 Hz, $PhC{\equiv}CCH(OH)CH_3$), 1.90 (br, 1H, $PhC{\equiv}CCH(OH)CH_3$), 4.78 (q, 1H, *J* = 6.7 Hz, $PhC{\equiv}CCH(OH)CH_3$), 7.30 – 7.33 (m, 3H, Ar-*H* Ph), 7.43 – 7.45 (m, 2H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.4, 58.9, 84.0, 90.9, 122.6, 128.3, 128.4, 131.7. All analytical data is in accordance with reported literature values.[180]

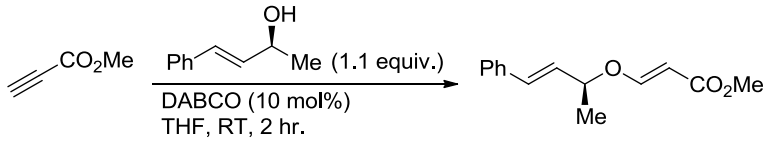
(*S*,*E*)-4-Phenylbut-3-en-2-ol (428)



To a stirred solution of Red-Al (1.22 mL, 5.44 mmol, 1.6 equiv.) in ether (30 mL) at 0 °C was added a solution of (*S*)-4-phenylbut-3-yn-2-ol **432** (0.5 g, 3.4 mmol, 1 equiv.) in ether (20 mL) dropwise. After 10 minutes the ice bath was removed and the mixture

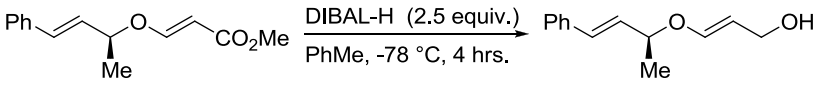
stirred at room temperature for 4 hours. Saturated NH_4Cl (20 mL) was added before diluting with ether (10 mL), NaOH (1M, 10 mL) and water (10 mL). The layers were separated, and the aqueous phase extracted with ether (3 x 50 mL). Organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification was achieved by flash chromatography (DCM) to afford the title compound as a colourless solid (1.62 g, 97%). $[\alpha]_D^{20}$ -31° (*c* 1, DCM); MP: 28 – 29 °C, Lit: 29 – 30 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ: 1.37 (d, 3H, *J* = 6.6 Hz, PhCH=CHCH(C*H*$_3$)OH), 4.47 – 4.52 (m, 1H, PhCH=CHC*H*(CH_3)OH), 6.31 (dd, 1H, *J* = 15.6, 6.4 Hz, PhCH=C*H*CH(CH_3)OH), 6.60 (d, 1H, *J* = 15.6 Hz, PhC*H*=CHCH(CH_3)OH), 7.25 – 7.43 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, CD_2Cl_2) δ: 23.6, 68.7, 126.3, 127.5, 128.5, 128.9, 133.9, 136.9. All analytical data is in accordance with reported literature values.[181]

(*E*)-Methyl 3-((*S*,*E*)-4-phenylbut-3-en-2-yloxy)acrylate (433)



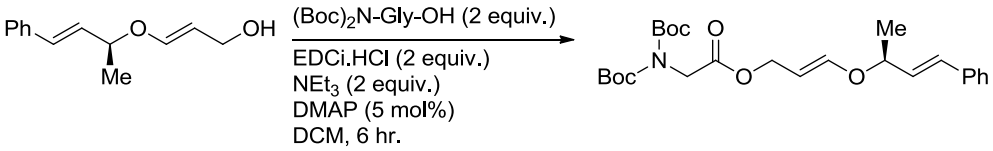
(*S*,*E*)-4-phenylbut-3-en-2-ol **428** (1.62 g, 10.9 mmol, 1.1 equiv.) in THF (400 mL) was added DABCO (0.12 g, 0.99 mmol, 0.1 equiv.) and methyl propiolate **232** (1.00 mL, 9.93 mmol, 1 equiv.) were combined according to the general procedure (reaction time 2 hours). Purification was achieved by flash chromatography (15:1 Pet/EtOAc) to afford title compound as a colorless oil (1.65 g, 65%). $[\alpha]_D^{20}$ -191° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 3028.5, 2983.8, 2950.9, 1706.9, 1637.8, 1619.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.49 (d, 3H, *J* = 6.4 Hz, PhCH=CHCH(C*H*$_3$)O), 3.70 (s, 3H, CO_2C*H*$_3$), 4.68 (pent, 1H, *J* = 7.0 Hz, PhCH=CHC*H*(CH_3)O), 5.34 (d, 1H, *J* = 11.2 Hz, OCH=C*H*CO_2CH_3), 6.17 (dd, 1H, *J* = 16.0, 7.0 Hz, PhCH=C*H*CH(C*H*$_3$)O), 6.61 (1H, *J* = 16.0 Hz, PhC*H*=CHCH(C*H*$_3$)O), 7.26 – 7.30 (m, 1H, Ar-*H* Ph), 7.33 – 7.36 (m, 2H, Ar-*H* Ph), 7.39 – 7.41 (m, 2H, Ar-*H* Ph), 7.60 (d, 1H, *J* = 11.2 Hz, OC*H*=CHCO_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 51.0, 79.7, 97.8, 126.7, 128.2, 128.4, 128.7, 132.4, 135.8, 161.4, 168.3; HRMS (ESI, +ve) *m/z*: calcd for $C_{14}H_{16}O_3Na$ 255.0997, found 255.0986. $(M+Na)^+$.

(*E*)-3-((*S*,*E*)-4-Phenylbut-3-en-2-yloxy)prop-2-en-1-ol (434)



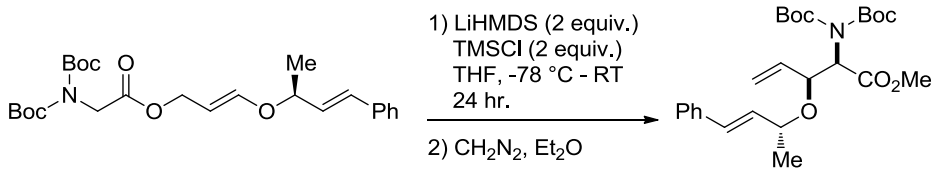
(*E*)-Methyl 3-((*S*,*E*)-4-phenylbut-3-en-2-yloxy)acrylate **433** (0.98 g, 4.22 mmol) was reduced according to general procedure 5, to afford the title compound as a colourless oil. (0.59 g, 68%). $[\alpha]_D^{20}$ -183° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 3393.9, 3026.0, 2976.6, 2871.7, 1669.0, 1649.9; ^{1}H NMR (500 MHz, d_6-acetone) δ: 1.38 (d, 3H, *J* = 6.5 Hz, PhCH=CHCH(C*H*$_3$)O), 3.97 (d, 2H, *J* = 7.0 Hz, OCH=CHC*H*$_2$OH), 4.53 (quin, 1H, *J* = 6.5 Hz, PhCH=CHC*H*(CH$_3$)O), 5.12 (dt, 1H, *J* = 12.6, 7.0 Hz, OCH=C*H*CH$_2$OH), 6.27 (dd, 1H, *J* = 15.5, 6.5 Hz, PhCH=C*H*CH(CH$_3$)O), 6.46 (d, 1H, *J* = 12.6 Hz, OC*H*=CHCH$_2$OH), 6.64 (d, 1H, *J* = 15.5 Hz, PhC*H*=CHCH(CH$_3$)O), 7.26 – 7.47 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ:20.7, 59.4, 76.7, 105.8, 126.5, 127.7, 128.6, 130.7, 130.8, 136.7, 147.5.

(*E*)-3-(((*S*,*E*)-4-phenylbut-3-en-2-yl)oxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (429)



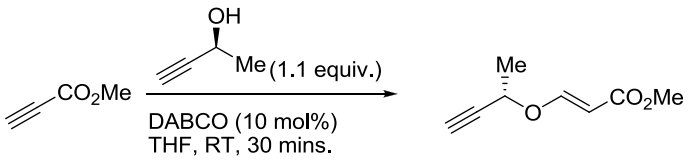
EDCi.HCl (0.62 g), triethylamine (0.44 mL), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.89 g) and (*E*)-3-((*S*,*E*)-4-phenylbut-3-en-2-yloxy)prop-2-en-1-ol **434** (0.33 g) were combined according to general procedure 3, to afford the title compound as a yellow oil (0.85 g, 50%). $[\alpha]_D^{20}$ -179° (*c* 1, DCM) ;FTIR (film/cm^{-1}) υ_{max}: 3024.8, 2989.7, 2985.2, 1753.7, 1734.4, 1699.3, 1652.4; ^{1}H NMR (500 MHz, d_6-acetone) δ: 1.40 (d, 3H, *J* = 7.3 Hz, OCH(C*H*$_3$)CH=CHPh), 1.48 (s, 18H, (C*H*$_3$)$_3$COCON), 3.00 (d, 2H, *J* = 7.7 Hz, OC*H*$_2$CH=CHO), 4.23 (s, 2H, NC*H*$_2$CO$_2$), 4.55 (app. d, 2H, *J* = 7.3 Hz, OC*H*(CH$_3$)CH=CHPh), 5.08 (dt, 1H, *J* = 12.9, 7.7 Hz, OCH$_2$C*H*=CHO), 6.27 (dd, 1H, *J* = 16.0, 7.3 Hz, OCH(CH$_3$)C*H*=CHPh), 6.65 – 6.70 (m, 2H, OCH$_2$CH=C*H*O & OCH(CH$_3$)CH=C*H*Ph), 7.26 – 7.48 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.6, 27.4, 47.1, 62.9, 77.4, 82.0, 99.5, 126.6, 128.6, 130.2, 131.3, 136.6, 152.3, 168.8; HRMS (ESI, +ve) *m/z*: calcd. for $C_{25}H_{35}NO_7Na$ 484.2311, found 484.2326 $(M+Na)^+$.

(2*R*,3*S*)-methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-(((*S*,*E*)-4-phenylbut-3-en-2-yl)oxy)pent-4-enoate (435)



(*E*)-3-(((*S*,*E*)-4-phenylbut-3-en-2-yl)oxy)allyl 2-(bis(tert-butoxycarbonyl)amino)acetate **429** (0.26 g, 0.55 mmol, 1 equiv.), TMSCl (0.14 mL, 1.1 mmol, 2 equiv.) and LiHMDS (1.11 mL, 1.1 mmol, 2 equiv.) were combined according to the general procedure. Treatment with diazomethane and purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) afforded the title compound as a colourless oil. (0.08 g, 30%). FTIR (film/cm^{-1}) υ_{max}: 3010.7, 2975.0, 1796.7, 1725.3, 1698.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.27 (d, 3H, *J* = 6.6 Hz, OCH(C*H*$_3$)CH), 1.54 (s, 18H, (C*H*$_3$)$_3$COCON), 3.72 (s, 3H, CO_2CH_3), 4.10 – 4.15 (m, 1H, OC*H*(CH$_3$)CH), 4.54 (dd, 1H, *J* = 8.8, 3.7 Hz, H_2C=CHC*H*O), 4.88 (d, 1H, *J* = 8.8 Hz, NC*H*CO_2), 5.01 – 5.17 (m, 2H, *H*$_2$C=CHCH(CH$_3$)O), 5.26 – 5.42 (m, 2H, *H*$_2$C=CHCHO), 5.65 (ddd, 1H, *J* = 17.9, 9.9, 7.4 Hz, H_2C=C*H*CHO), 6.27 (dd, 1H, *J* = 16.0, 7.3 Hz, OCH(CH$_3$)C*H*=CHPh), 6.65 – 6.70 (m, 2H, OCH_2CH=C*H*O & OCH(CH$_3$)CH=C*H*Ph), 7.22 – 7.39 (m, 5H, Ar-*H* Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.7, 28.0, 51.9, 62.0, 75.7, 82.8, 82.9, 117.3, 126.4, 127.4, 128.5, 129.7, 132.4, 138.0, 152.3, 169.4; HRMS (ESI, +ve) *m/z*: calcd. for $C_{26}H_{37}NO_7Na$ 498.2468, found 498.2487 $(M+Na)^+$.

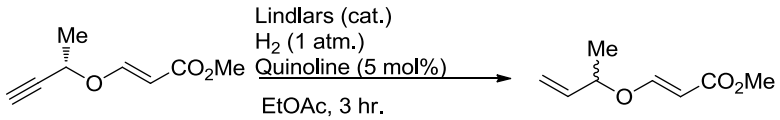
(*S*,*E*)-Methyl 3-(but-3-yn-2-yloxy)acrylate (437)



DABCO (0.40 g, 3.15 mmol) in THF (250 mL), *S*-butyn-2-ol **(*S*)-189** (2.43 g, 34.7 mmol) and methyl propiolate **232** (3.1 mL, 31.5 mmol) were combined according to the general procedure. Purification was achieved by flash chromatography (15:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (4.67 g, 87%). $[\alpha]_D^{20}$ -169° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 2994.4, 2952.8, 2117.7, 1708.0, 1644.4, 1623.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.59 (d, 3H, *J* = 6.7 Hz, HCCCH(C*H*$_3$)O), 2.59 (d, 1H, *J* = 2.2 Hz, *H*CCCH(CH$_3$)O), 3.72 (s, 3H, CO_2CH_3), 4.68 (dq, 1H, *J* = 6.7, 2.2 Hz, HCCC*H*(CH$_3$)O), 5.40 (d, 1H, *J* = 12.5 Hz, OCHC*H*CO_2CH_3), 7.61 (d, 1H, *J* = 12.5

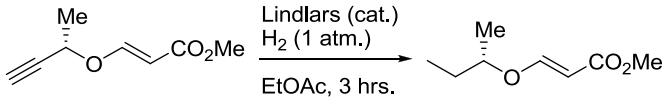
Hz, OC*H*CHCO$_2$CH$_3$);^{13}C NMR (125 MHz, CDCl$_3$) δ: 21.6, 51.2, 67.0, 75.4, 80.9, 98.8, 160.0, 167.9; HRMS (ESI, +ve) *m/z*: calcd for $C_8H_{10}O_3Na$ 177.0528, found 177.0536 $(M+Na)^+$.

(*S,E*)-Methyl 3-(but-3-en-2-yloxy)acrylate (*rac*-426)



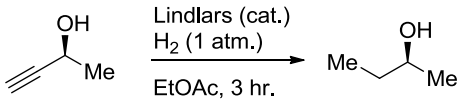
To a solution of (*S,E*)-methyl 3-(but-3-yn-2-yloxy)acrylate **437** (1.00 g, 6.49 mmol) in EtOAc (40 mL) was added Lindlars catalyst (0.90 g) and quinoline (5 drops) under 1 atmosphere of hydrogen for 3 hours. The solution was filtered through celite and concentrated *in vacuo* to afford the crude product. Purification was achieved by flash chromatography (15:1 Pet/EtOAc) to afford the title compound as a colourless oil. (0.80 g, .98%). FTIR (film/cm^{-1}) υ_{max}: 2985.6, 2951.9, 1705.8, 1639.2, 1621.1; ^{1}H NMR (500 MHz, CDCl$_3$) δ:1.39 (d, 3H, *J* = 6.1 Hz, CH$_2$CHCH(C*H*$_3$)O), 3.70 (s, 3H, CO$_2$C*H*$_3$), 4.50 (quin, 1H, *J* = 6.1 Hz, CH$_2$CHC*H*(CH$_3$)O), 5.23 – 5.30 (m, 3H, C*H*$_2$CHCH(C*H*$_3$)O & OCHC*H*CO$_2$CH$_3$), 5.82 (ddd, 1H, *J* = 17.0, 9.6, 6.1 Hz, CH$_2$C*H*CH(C*H*$_3$)O), 7.53 (d, 1H, *J* = 12.1 Hz, OC*H*CHCO$_2$CH$_3$);^{13}C NMR (125 MHz, CDCl$_3$) δ: 20.7, 51.0, 79.6, 97.6, 117.2, 137.5, 161.4, 168.4; HRMS (ESI, +ve) *m/z*: calcd for $C_8H_{12}O_3Na$ 179.0684, found 179.0685 $(M+Na)^+$.

(*S,E*)-Methyl 3-*sec*-butoxyacrylate (438)



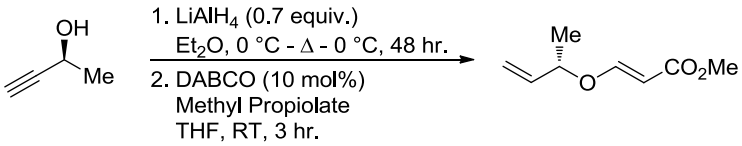
To a solution of (*S,E*)-methyl 3-(but-3-yn-2-yloxy)acrylate **437** (0.15 g, 0.94 mmol) in EtOAc (10 mL) was added Lindlars catalyst (0.15 g) under 1 atmosphere of hydrogen for 3 hours. The solution was filtered through celite and concentrated *in vacuo* to afford the title compound as a colourless oil (0.11 g, 74%). $[\alpha]_D^{20}$ +18° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 2987.1, 1706.8, 1635.7, 1631.9; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.27 (d, 3H, *J* = 6.2 Hz, CH$_3$CH$_2$CH(C*H*$_3$)O), 1.54 – 1.72 (m, 2H, CH$_3$C*H*$_2$CH(CH$_3$)O), 3.70 (s, 3H, CO$_2$C*H*$_3$), 3.99 (sext, 1H, *J* = 6.2 Hz, CH$_3$CH$_2$C*H*(CH$_3$)O), (5.25 (d, 1H, *J* = 12.3 Hz, OCHC*H*CO$_2$CH$_3$), 7.55 (d, 1H, *J* = 12.3 Hz, OC*H*CHCO$_2$CH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 9.5, 19.5, 29.1, 51.0, 81.1, 96.7, 162.3, 168.7; HRMS (ESI, +ve) *m/z*: calcd. for $C_8H_{14}O_3Na$ 181.0841, found 181.0856 $(M+Na)^+$.

(S)-Butan-2-ol (439)



To a solution of (*S*)-butynol **(*S*)-189** (0.07 g, 1.00 mmol) in EtOAc (10 mL) was added Lindlars catalyst (0.05 g) under 1 atmosphere of hydrogen for 3 hours. The solution was filtered through celite and concentrated *in vacuo* to afford the title compound as a colourless oil (0.0.7 g, 100%). $[\alpha]_D^{20}$ +12° (*c* 1, MeCN); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.93 (t, 3H, *J* = 7.5 Hz, C*H*$_3$CH$_2$), 1.18 (d, 3H, *J* = 6.2 Hz, CH(OH)C*H*$_3$), 1.40 (br, 1H, O*H*), 1.42 – 1.52 (m, 2H, CH$_3$C*H*$_2$CH) , 3.67 – 3.78 (m, 1H, CH$_2$C*H*(OH)CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.6, 22.3, 31.6, 68.7. All analytical data is in accordance with reported literature values.[182]

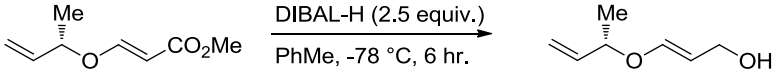
(*S*,*E*)-Methyl 3-(but-3-en-2-yloxy)acrylate (426)



To a round-bottom flask equipped with a condenser is added lithium aluminium hydride (0.95 g, 25.0 mmol, 0.7 equiv.). Ether (50 mL) was added and the resulting suspension vigorously stirred and cooled to 0 °C. A solution of (*S*)-butyn-2-ol **(*S*)-189** (2.83 mL, 35.7 mmol, 1 equiv.) in ether (20 mL) was added *via* syringe pump over 5 minutes. The solution was brought to a gentle reflux for 48 hours. The mixture was then cooled to 0 °C and saturated Rochelle's salt solution was added dropwise until gas evolution stopped. A further 60 mL of ether was added and the white precipitate removed by filtration through a pad of celite, then washed with an additional 60 mL of ether. The resultant filtrate was concentrated *in vacuo*. Purification was achieved by Kugelrohr bulb-to-bulb distillation at 52 °C and 16 torr to afford (*S*)-3-buten-2-ol as a colourless oil (1.00 g, 40%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.30 (d, 3H, *J* = 6.5 Hz, H$_2$C=CHCH(OH)C*H*$_3$), 4.33 (qt, 1H, *J* = 6.5, 1.5 Hz, H$_2$C=CHC*H*(OH)CH$_3$), 5.09 (dt, 1H, *J* = 10.8, 1.3 Hz, *H*$_2$C=CHCH(OH)CH$_3$), 5.24 (dt, 1H, *J* = 16.6, 1.3 Hz, *H*$_2$C=CHCH(OH)CH$_3$), 5.94 (ddd, 1H, *J* = 16.6, 10.8, 6.5 Hz, H$_2$C=C*H*CH(OH)CH$_3$). All analytical data is in accordance with reported literature values.[183]

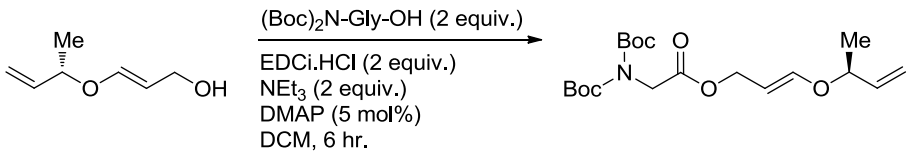
DABCO (0.13 g, 1.19 mmol) in THF (200 mL), (*S*)-3-buten-2-ol (1.00 g, 11.9 mmol) and methyl propiolate (1.3 mL, 11.9 mmol) were combined according to general procedure 4. Purification was achieved by flash chromatography (20:1 Pet/EtOAc) to afford the title compound as a colourless oil (1.24 g, 60%). $[\alpha]_D^{20}$ -128° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 3085.4, 2985.1, 2952.1, 1708.4, 1639.1, 1620.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (d, 3H, *J* = 6.6 Hz, H_2C=CHCH(C*H*$_3$)O), 3.68 (s, 3H, CO_2CH_3), 4.48 (quin, 1H, *J* = 6.6 Hz, H_2C=CHC*H*(CH_3)O), 5.21 – 5.28 (m, 3H, *H*$_2$C=CHCH(CH_3)O & OCH=C*H*CO_2CH_3), 5.80 (ddd, 1H, *J* = 17.2, 10.8, 6.6 Hz, H_2C=C*H*CH(CH_3)O), 7.52 (d, 1H, *J* = 17.2 Hz, OC*H*=CHCO_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.7, 51.1, 79.7, 97.7, 117.2, 137.5, 161.4, 168.4; HRMS (ESI, +ve) *m/z* calcd. for $C_8H_{12}O_3Na$ 179.0684, found 179.0676 $(M+Na)^+$.

(*S*,*E*)-3-(But-3-en-2-yloxy)prop-2-en-1-ol (425)



(*S*,*E*)-Methyl 3-(but-3-en-2-yloxy)acrylate **426** (0.85 g, 5.44 mmol) was reduced according to general procedure 5, to afford the title compound as a yellow oil (0.56 g, 80%). $[\alpha]_D^{20}$ -129° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 3348.9, 2980.5, 2871.7, 1669.5, 1652.1; ^{1}H NMR (500 MHz, d_6-acetone) δ: 1.26 (d, 3H, *J* = 6.6 Hz, H_2C=CHCH(C*H*$_3$)O), 3.35 (t, 1H, *J* = 5.6 Hz, OCH=CHCH$_2$O*H*), 3.93 (ddd, 2H, *J* = 6.9, 5.6, 1.4 Hz, OCH=CHC*H*$_2$OH), 4.35 (qt, 1H, *J* = 6.6, 1.3 Hz, H_2C=CHC*H*(CH_3)O), 5.00 – 5.05 (m, 1H, OCH=C*H*CH$_2$OH), 5.13 (dt, 1H, *J* = 10.3, 1.3 Hz, *H*$_2$C=CHCH(CH_3)O), 5.25 (dt, 1H, *J* = 17.4, 1.3 Hz, *H*$_2$C=CHCH(CH_3)O), 5.82 (ddd, 1H, *J* = 17.4, 10.3, 6.6 Hz, H_2C=C*H*CH(CH_3)O), 6.37 (dt, 1H, *J* = 12.3, 1.3 Hz, OC*H*=CHCH$_2$OH); ^{13}C NMR (125 MHz, d_6-acetone) δ: 20.2, 59.3, 76.7, 105.7, 114.9, 139.5, 147.4.

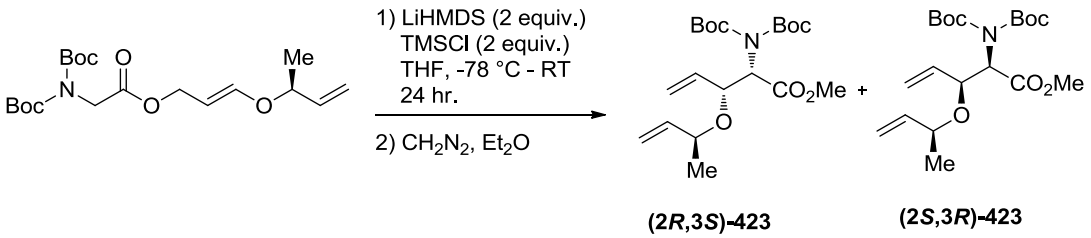
(*S*,*E*)-3-(But-3-en-2-yloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate (424)



EDCi.HCl (0.43 g, 2.24 mmol), triethylamine (0.3 mL, 2.24 mmol), 2-(bis(*tert*-butoxycarbonyl)amido)acetic acid **305** (0.62 g, 2.24 mmol) and (*S*,*E*)-3-(but-3-en-2-yloxy)prop-2-en-1-ol **425** (0.14 g, 1.12 mmol) were combined according to general

procedure 3, to afford the title compound as a yellow oil (0.45 g, 98%). $[\alpha]_D^{20}$ -120° (*c*.1, DCM); 2979.4, 2937.1, 1797.9, 1755.8, 1735.6, 1697.6, 1671.4; ^{1}H NMR (500 MHz, d_6-acteone) δ: 1.29 (d, 3H, *J* = 6.2 Hz, OCH(C*H*$_3$)CH=CH$_2$), 1.49 (s, 18H, (C*H*$_3$)$_3$COCON), 4.28 (s, 2H, NC*H*$_2$CO$_2$), 4.44 (quin, 1H, *J* = 6.2 Hz, OC*H*(CH$_3$)CH=CH$_2$), 4.54 (d, 2H, *J* = 7.8 Hz, OC*H*$_2$CH=CHO), 5.03 (dt, 1H, *J* = 12.6, 7.8 Hz, OCH$_2$C*H*=CHO), 5.16 (dt, 1H, *J* = 10.6, 1.2 Hz, OCH(CH$_3$)CH=C*H*$_2$), 5.27 (dt, 1H, *J* = 17.3, 1.2 Hz, OCH(CH$_3$)CH=C*H*$_2$), 5.84 (ddd, 1H, *J* = 17.3, 10.6, 6.2 Hz, OCH(CH$_3$)C*H*=CH$_2$), 6.62 (d, 1H, *J* = 12.6 Hz, OCH$_2$CH=C*H*O); ^{13}C NMR (125 MHz, d_6-acteone) δ: 20.1, 27.2, 29.7, 47.0, 62.9, 77.3, 82.1, 99.3, 115.3, 139.0, 151.7, 151.8; HRMS (ESI, +ve) *m/z*: calcd. for $C_{19}H_{31}NO_7Na$ 408.1998, found 408.1995 $(M+Na)^+$.

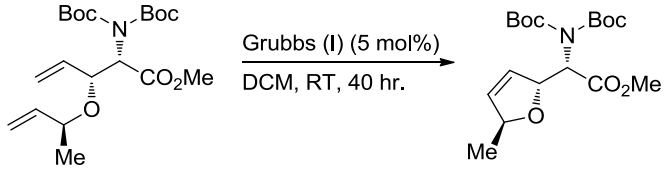
(2*S*,3*R*)-Methyl 3-((*S*)-but-3-en-2-yloxy)-2-(bis(*tert*-butoxycarbonyl)amino)pent-4-enoate (423)



(*S*,*E*)-3-(But-3-en-2-yloxy)allyl 2-(bis(*tert*-butoxycarbonyl)amino)acetate **424** (0.20 g, 0.27 mmol), TMSCl (0.07 mL, 0.55 mmol) and LiHMDS (0.55 mL, 0.55 mmol) were combined according to general procedure 7. Treatment with diazomethane and purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt$_3$) afforded the title compound as a colourless oil (0.11 g, 60%, dr 2.5:1). $[\alpha]_D^{20}$ -122° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 2981.5, 2938.2, 1751.3, 1699.9; ^{1}H NMR (500 MHz, d_6-acetone) δ **(2*R*,3*S*)-423**: 1.18 (d, 3H, *J* = 6.4 Hz, H$_2$C=CHCH(C*H*$_3$)O), 1.51 (s, 18H, (C*H*$_3$)$_3$COCON), 3.68 (s, 3H, CO$_2$C*H*$_3$), 3.92 – 3.99 (m, 1H, H$_2$C=CHC*H*(CH$_3$)O), 4.49 – 4.53 (m, 1H, H$_2$C=CHC*H*O), 4.80 (d, 1H, *J* = 8.4 Hz, NC*H*CO$_2$), 5.01 – 5.17 (m, 2H, *H*$_2$C=CHCH(CH$_3$)O), 5.26 – 5.42 (m, 2H, *H*$_2$C=CHCHO), 5.77 (ddd, 1H, *J* = 16.7, 10.6, 6.6 Hz, H$_2$C=C*H*CHO), 6.09 (ddd, 1H, *J* = 16.3, 10.8, 6.8 Hz, H$_2$C=C*H*CH(CH$_3$)O); δ**(2*S*,3*R*)-423**: 1.16 (d, 3H, *J* = 6.4 Hz, H$_2$C=CHCH(C*H*$_3$)O), 1.50 (s, 18H, (C*H*$_3$)$_3$COCON), 3.66 (s, 3H, CO$_2$C*H*$_3$), 3.92 – 3.99 (m, 1H, H$_2$C=CHC*H*(CH$_3$)O), 4.44 – 4.47 (m, 1H, H$_2$C=CHC*H*O), 4.80 (d, 1H, *J* = 8.4 Hz, NC*H*CO$_2$), 5.01 – 5.17 (m, 2H, *H*$_2$C=CHCH(CH$_3$)O), 5.26 – 5.42 (m, 2H, *H*$_2$C=CHCHO), 5.65 (ddd, 1H, *J* = 17.9, 9.9, 7.4 Hz, H$_2$C=C*H*CHO), 6.01 (ddd, 1H, *J* =

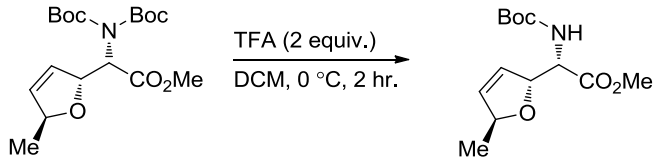
17.1, 10.8, 6.4 Hz, H_2C=C*H*CH(CH_3)O); ^{13}C NMR (125 MHz, d_6-acetone) δ**(2*R*,3*S*)-423**:19.8, 27.3, 51.3, 62.0, 74.2, 74.8, 82.2, 113.9, 115.8, 138.3, 140.9, 152.3, 168.8; δ**(2*S*,3*R*)-423**: 21.4, 27.2, 51.2, 61.9, 74.0, 75.7, 82.0, 115.9, 116.7, 137.6, 140.5, 152.0, 168.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_{20}H_{34}NO_7$ 400.2335, found 400.2324 $(M+H)^+$.

(*S*)-Methyl 2-(bis(*tert*-butoxycarbonyl)amino)-2-((2*R*,5*S*)-5-methyl-2,5-dihydrofuran-2-yl)acetate (436)



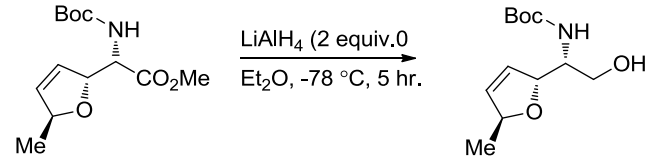
To a solution of (2*S*,3*R*)-methyl 3-((*S*)-but-3-en-2-yloxy)-2-(bis(*tert*-butoxycarbonyl)amino)pent-4-enoate **423** (0.10 g, 0.25 mmol, 1 equiv.) in DCM (5 mL) was added bis(tricyclohexylphosphine)benzylidine ruthenium (IV) chloride (0.04 g, 0.005 mmol, 0.05 equiv.) and stirred at room temperature for 40 hours. The mixture was passed through a pad of celite and concentrated *in vacuo*. Purification was achieved by flash chromatography (15:1 Pet/EtOAc + 1% NEt_3) to afford the title compound as a colourless oil (0.08 g, 85%, dr 2.5:1). $[\alpha]_D^{20}$ -70° (*c* 1, DCM); FTIR (film/cm^{-1}) υ_{max}: 2984.6, 1747.1, 1698.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ_{major}: 1.23 (d, 3H, *J* = 6.4 Hz, CH(C*H*$_3$)O), 1.52 (s, 18H, (C*H*$_3$)$_3$COCON), 3.73 (s, 3H, CO_2C*H*$_3$), 4.85 (d, 1H, J = 8.7 Hz, NC*H*CO_2), 4.90 – 4.95 (m, 1H, HC=CHC*H*O), 5.27 – 5.30 (m, 1H, CHC*H*(CH_3)O), 5.85 – 5.87 (m, 1H, HC=C*H*CH(CH_3)O), 6.15 – 6.18 (m, 1H, HC=C*H*CHO); δ_{minor}: 1.25 (d, 3H, *J* = 6.4 Hz, CH(C*H*$_3$)O), 1.52 (s, 18H, (C*H*$_3$)$_3$COCON), 3.73 (s, 3H, CO_2C*H*$_3$), 4.76 (d, 1H J = 8.4 Hz, NC*H*CO_2), 4.79 – 4.83 (m, 1H, HC=CHC*H*O), 5.31 – 5.33 (m ,1H, CHC*H*(CH_3)O), 5.85 – 5.87 (m, 1H, HC=C*H*CH(CH_3)O), 6.15 – 6.18 (m, 1H, HC=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ_{major}: 22.1, 28.0, 51.9, 63.3, 82.3, 83.0, 83.6, 128.7, 132.9, 152.4, 169.6; δ_{minor}: 21.4, 28.0, 51.9, 62.3, 81.3, 82.9, 83.3, 128.9, 133.1, 152.2, 169.6; HRMS (ESI, +ve) *m/z*: calcd. for $C_{18}H_{29}NO_7Na$ 394.1842, found 394.1857 $(M+Na)^+$.

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-2-((2*R*,5*S*)-5-methyl-2,5-dihydrofuran-2-yl)acetate (442)



To a stirred solution of (*S*)-methyl 2-(bis(*tert*-butoxycarbonyl)amino)-2-((2*R*,5*S*)-5-methyl-2,5-dihydrofuran-2-yl)acetate **436** (0.04g, 0.10 mmol, 1 equiv.) in DCM (5 mL) was added TFA (0.02 mL, 2 equiv.) at 0 °C. The mixture was stirred for 2 hourd before concentrating *in vacuo*. The residue was taken up in saturated sodium bicarbonate solution (10 mL) and extracted with EtOAc (4 × 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification was achieved by flash chromatography (4:1 Pet/EtOAc) to afford the title compound as a colourless oil (0.02 g, 79%).^{1}H NMR (500 MHz, d_6-Acetone) δ_{major}: 1.21 (d, 3H, *J* = 6.4 Hz, CH(C*H*$_3$)O), 1.43 (s, 18H, (C*H*$_3$)$_3$COCON), 3.73 (s, 3H, CO_2CH_3), 4.85 (d, 1H, *J* = 8.7 Hz, NC*H*CO_2), 4.90 (br, 1H, N*H*), 4.92 – 4.95 (m, 1H, HC=CHC*H*O), 5.27 – 5.30 (m, 1H, CHC*H*(CH$_3$)O), 5.85 – 5.87 (m, 1H, HC=C*H*CH(CH$_3$)O), 6.15 – 6.18 (m, 1H, HC=C*H*CHO); ^{13}C NMR (125 MHz, d_6-Acetone) δ_{major}: 21.3, 27.6, 51.5, 56.2, 78.6, 82.3, 86.6, 126.5, 133.3, 155.2, 170.4.

***N*-Boc furanomycinol (421)**



To a stirred solution of lithium aluminium hydride (0.005 g, 0.13 mmol, 2 equiv.) in ether (5 mL) at -78 °C was added a solution of (*S*)-methyl 2-((*tert*-butoxycarbonyl)amino)-2-((2*R*,5*S*)-5-methyl-2,5-dihydrofuran-2-yl)acetate **442** (0.02 g, 0.07 mmol) in ether (3 mL). The mixture was stirred at -78 °C for 5 hours before quenching by the addition of EtOAc, then poured onto ice-cold saturated Rochelle salt solution (100 mL) followed by the addition of further EtOAc (100 mL). The biphasic mixture was vigorously stirred at 0 °C for 2 hours before separating and extracting with EtOAc (3 × 10 mL). The organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification was achieved by flash chromatography (Pet/EtOAc 1:1) to afford the title compound as a colourless oil (0.01 g, 65%). FTIR (film/cm^{-1}) υ_{max}: 3447.8, 3395.6, 2984.3, 2841.3, 1700.4, 1517.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ_{major}: 1.32 (d, 3H, *J* = 6.5

Hz, CH(C*H*$_3$)O), 1.43 (s, 9H, (C*H*$_3$)$_3$COCON), 2.74 (br, 1H, O*H*), 3.72 – 3.92 (m, 3H,CHC*H*$_2$OH & N*H*)), 4.92 – 5.11 (m, 2H, HC=CHC*H*O & NC*H*CO$_2$), 5.76 – 5.89 (m, 2H, *H*C=C*H*CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ_{major}: 21.8, 28.4, 52.9, 65.1, 79.3, 82.6, 88.7, 127.5, 132.5, 157.0; HRMS (ESI, +ve) *m/z*: calcd. for $C_{18}H_{29}NO_7Na$ 394.1842, found 394.1857 $(M+Na)^+$. All analytical data is in accordance with reported literature values.[152]

CHAPTER 7 APPENDICES

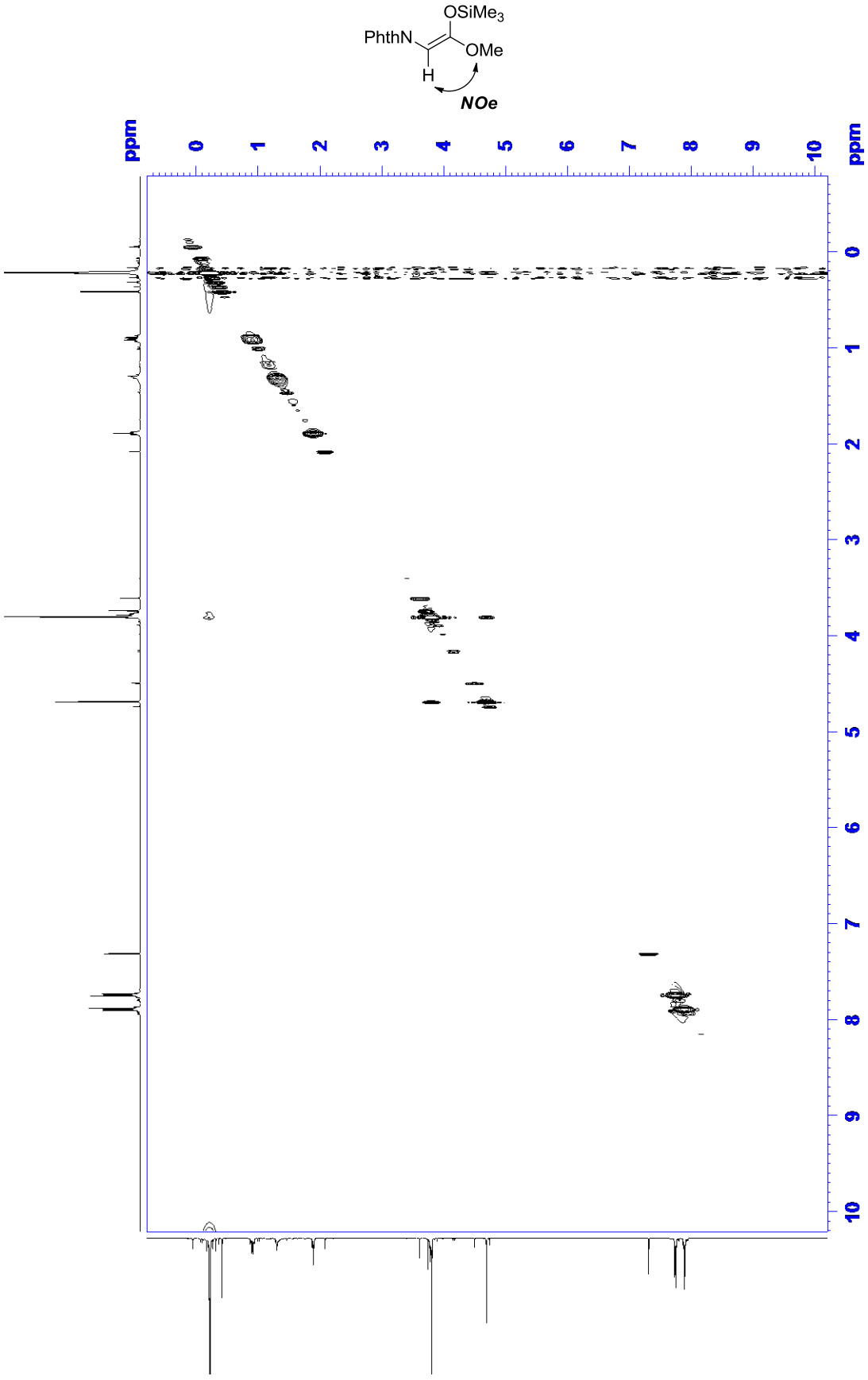
7.1 AMINO ACIDS

Table 1: Trivial names and symbols for proteinogenic amino acids[6]

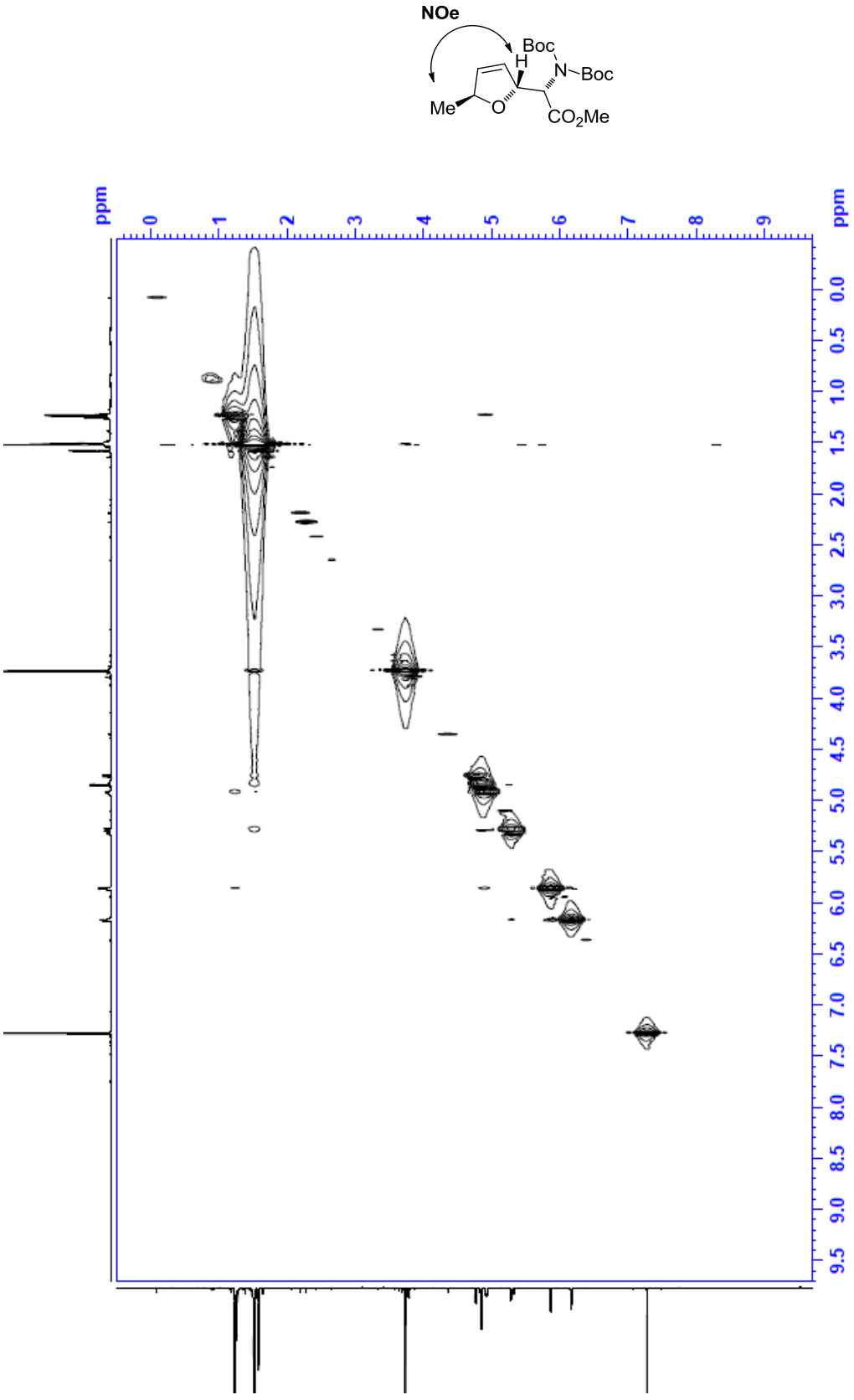
Trivial Name	Symbol	Trival Name	Symbol
Alanine	Ala	Leucine	Leu
Arginine	Arg	Lysine	Lys
Asparagine	Asn	Methionine	Met
Aspartic Acid	Asp	Phenylalanine	Phe
Cysteine	Cys	Proline	Pro
Glutamine	Gln	Serine	Ser
Glutamic Acid	Glu	Theronine	Thr
Glycine	Gly	Tryptophan	Trp
Histidine	His	Tyrosine	Tyr
Isoleucine	Lle	Valine	Val

7.2 NMR

7.2.1 *NOeSY spectra of (E)- and (Z)-SKA of ester 232*



7.2.2 *NOeSY spectra of 436*



7.3 X-RAY

Table 2: Crystal data and structure refinement for Cs Carboxylate 292

Identification code	h08dc1
Empirical formula	C_{14} H_{16} Cs N O_7
Formula weight	443.19
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2_1/a
Unit cell dimensions	a = 7.6258(2) Å α= 90°
	b = 13.1985(3) Å β = 100.5660(10)°
	c = 16.3312(5) Å γ = 90°
Volume	1615.85(7) $Å^3$
Z	4
Calculated density	1.822 Mg/m^3
Absorption coefficient	2.326 mm^{-1}
F(000)	872
Crystal size	0.45 x 0.25 x 0.15 mm
Theta range for data collection	3.56 to 27.51°
Limiting indices	-9<=h<=9, -17<=k<=16, -21<=l<=21
Reflections collected	21615
Reflections unique	3699 [R(int) = 0.0544]
Completeness to theta	27.51 (99.5%)
Max. transmission	0.7217
Min. transmission	0.4208
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3699 / 2 / 225
Goodness-of-fit on F^2	1.064
Final R indices [I>2σ(I)]	R^1 = 0.0329, wR_2 = 0.0774
R indices (all data)	R^1 = 0.0429, wR_2 = 0.0831
Largest diff. peak and hole	1.494 and -1.189 $eÅ^{-3}$

Table 3: Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (A^2 × 10^3) for 292.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	X	Y	Z	U(eq)
Cs	5126(1)	1543(1)	437(1)	39(1)
N	9057(3)	323(2)	2940(1)	22(1)
O(1)	7990(3)	1688(2)	2116(1)	29(1)
O(2)	10603(3)	-671(2)	4002(1)	30(1)
O(3)	7110(3)	-438(2)	946(1)	33(1)
O(4)	9997(3)	-168(2)	1403(1)	33(1)
O(5)	6196(3)	-558(2)	3382(1)	31(1)
O(6)	2796(4)	1172(3)	1762(2)	56(1)
O(7)	9198(5)	1261(2)	5(2)	50(1)
C(1)	8911(4)	1347(2)	2744(2)	23(1)
C(2)	10054(4)	1894(2)	3441(2)	22(1)
C(3)	10390(4)	2915(2)	3572(2)	26(1)
C(4)	11481(4)	3193(2)	4316(2)	28(1)
C(5)	12203(4)	2478(2)	4908(2)	30(1)
C(6)	11869(4)	1446(2)	4769(2)	28(1)
C(7)	10798(4)	1172(2)	4028(2)	23(1)
C(8)	10204(4)	156(2)	3703(2)	24(1)
C(9)	8196(4)	-500(2)	2422(2)	23(1)
C(10)	8436(4)	-350(2)	1506(2)	25(1)
C(11)	6234(4)	-648(2)	2509(2)	23(1)
C(12)	4439(4)	-631(3)	3556(2)	36(1)
C(13)	5578(4)	-1673(2)	2193(2)	32(1)
C(14)	4100(5)	-1828(3)	1656(2)	44(1)

Table 4: Bond lengths [Å] for 292

Cs-O(3)#1	2.953(2)	O(7)-H(7B)	0.81(2)
Cs-O(7)#2	3.036(3)	C(1)-C(2)	1.487(4)
Cs-O(3)	3.059(2)	C(2)-C(3)	1.381(4)
Cs-O(6)	3.082(3)	C(2)-C(7)	1.397(4)
Cs-O(1)	3.183(2)	C(3)-C(4)	1.390(4)
Cs-O(7)	3.329(3)	C(3)-H(3)	0.9500
Cs-C(14)#1	3.593(4)	C(4)-C(5)	1.390(5)
Cs-C(10)	3.749(3)	C(4)-H(4)	0.9500
Cs-Cs#1	4.3091(4)	C(5)-C(6)	1.397(4)
Cs-Cs#3	4.5733(3)	C(5)-H(5)	0.9500
Cs-Cs#2	4.5733(3)	C(6)-C(7)	1.378(4)
Cs-H(6B)	3.25(6)	C(6)-H(6)	0.9500
Cs-H(7B)	3.37(5)	C(7)-C(8)	1.482(4)
N-C(1)	1.388(4)	C(9)-C(11)	1.540(4)
N-C(8)	1.402(4)	C(9)-C(10)	1.553(4)
N-C(9)	1.457(3)	C(9)-H(9)	1.0000
O(1)-C(1)	1.218(4)	C(11)-C(13)	1.500(4)
O(2)-C(8)	1.211(4)	C(11)-H(11)	1.0000
O(3)-C(10)	1.239(4)	C(12)-H(12A)	0.9800
O(3)-Cs#1	2.953(2)	C(12)-H(12B)	0.9800
O(4)-C(10)	1.256(4)	C(12)-H(12C)	0.9800
O(5)-C(12)	1.423(4)	C(13)-C(14)	1.311(5)
O(5)-C(11)	1.436(3)	C(13)-H(13)	0.9500
O(6)-H(6A)	0.75(7)	C(14)-Cs#1	3.593(4)
O(6)-H(6B)	0.81(6)	C(14)-H(14A)	0.9500
O(7)-Cs#3	3.036(3)	C(14)-H(14B)	0.9500
O(7)-H(7A)	0.842(19)		

Table 5: Bond angles [°] for 292

O(3)#1-Cs-O(7)#2	102.52(7)	Cs#2-Cs-H(7B)	162.6(7)
O(3)#1-Cs-O(3)	88.44(6)	H(6B)-Cs-H(7B)	137.6(12)
O(7)#2-Cs-O(3)	164.15(8)	C(1)-N-C(8)	111.6(2)
O(3)#1-Cs-O(6)	97.60(7)	C(1)-N-C(9)	125.7(2)
O(7)#2-Cs-O(6)	100.08(8)	C(8)-N-C(9)	22.7(2)
O(3)-Cs-O(6)	89.61(7)	C(1)-O(1)-Cs	154.37(19)
O(3)#1-Cs-O(1)	153.79(6)	C(10)-O(3)-Cs#1	152.8(2)
O(7)#2-Cs-O(1)	103.69(7)	C(10)-O(3)-Cs	114.66(18)
O(3)-Cs-O(1)	65.81(5)	Cs#1-O(3)-Cs	91.56(6)
O(6)-Cs-O(1)	78.29(7)	C(12)-O(5)-C(11)	112.6(2)
O(3)#1-Cs-O(7)	102.28(7)	Cs-O(6)-H(6A)	120(5)
O(7)#2-Cs-O(7)	104.16(8)	Cs-O(6)-H(6B)	94(4)
O(3)-Cs-O(7)	61.82(6)	H(6A)-O(6)-H(6B)	118(6)
O(6)-Cs-O(7)	144.24(8)	Cs#3-O(7)-Cs	91.75(7)
O(1)-Cs-O(7)	70.74(7)	Cs#3-O(7)-H(7A)	125(4)
O(3)#1-Cs-C(14)#1	59.80(7)	Cs-O(7)-H(7A)	129(3)
O(7)#2-Cs-C(14)#1	75.59(9)	Cs#3-O(7)-H(7B)	120(4)
O(3)-Cs-C(14)#1	100.88(8)	Cs-O(7)-H(7B)	86(4)
O(6)-Cs-C(14)#1	154.35(9)	H(7A)-O(7)-H(7B)	101(5)
O(1)-Cs-C(14)#1	127.37(7)	O(1)-C(1)-N	124.3(3)
O(7)-Cs-C(14)#1	59.19(8)	O(1)-C(1)-C(2)	129.1(3)
O(3)#1-Cs-C(10)	105.77(6)	N-C(1)-C(2)	106.6(2)
O(7)#2-Cs-C(10)	148.57(8)	C(3)-C(2)-C(7)	121.2(3)
O(3)-Cs-C(10)	17.47(6)	C(3)-C(2)-C(1)	131.2(3)
O(6)-Cs-C(10)	89.57(7)	C(7)-C(2)-C(1)	107.5(2)
O(1)-Cs-C(10)	48.83(6)	C(2)-C(3)-C(4)	117.2(3)
O(7)-Cs-C(10)	56.59(6)	C(2)-C(3)-H(3)	121.4
C(14)#1-Cs-C(10)	107.39(8)	C(4)-C(3)-H(3)	121.4
O(3)#1-Cs-Cs#1	45.20(5)	C(3)-C(4)-C(5)	121.8(3)
O(7)#2-Cs-Cs#1	146.24(6)	C(3)-C(4)-H(4)	119.1
O(3)-Cs-Cs#1	43.24(4)	C(5)-C(4)-H(4)	119.1

O(6)-Cs-Cs#1	94.92(6)	C(4)-C(5)-C(6)	120.8(3)
O(1)-Cs-Cs#1	108.90(4)	C(4)-C(5)-H(5)	119.6
O(7)-Cs-Cs#1	79.08(5)	C(6)-C(5)-H(5)	119.6
C(14)#1-Cs-Cs#1	77.84(6)	C(7)-C(6)-C(5)	117.3(3)
C(10)-Cs-Cs#1	60.61(4)	C(7)-C(6)-H(6)	121.3
O(3)#1-Cs-Cs#3	129.59(4)	C(5)-C(6)-H(6)	121.3
O(7)#2-Cs-Cs#3	68.39(6)	C(6)-C(7)-C(2)	121.6(3)
O(3)-Cs-Cs#3	95.82(4)	C(6)-C(7)-C(8)	130.2(3)
O(6)-Cs-Cs#3	132.53(6)	C(2)-C(7)-C(8)	108.2(2)
O(1)-Cs-Cs#3	61.74(4)	O(2)-C(8)-N	124.7(3)
O(7)-Cs-Cs#3	41.57(5)	O(2)-C(8)-C(7)	129.3(3)
C(14)#1-Cs-Cs#3	70.11(6)	N-C(8)-C(7)	106.1(2)
C(10)-Cs-Cs#3	82.99(4)	N-C(9)-C(11)	112.5(2)
C(10)-Cs-Cs#3	120.575(7)	N-C(9)-C(10)	110.1(2)
Cs#1-Cs-Cs#3	84.74(4)	C(11)-C(9)-C(10)	113.1(2)
O(3)#1-Cs-Cs#2	46.68(6)	N-C(9)-H(9)	106.9
O(7)#2-Cs-Cs#2	147.43(4)	C(11)-C(9)-H(9)	106.9
O(3)-Cs-Cs#2	79.08(5)	C(10)-C(9)-H(9)	106.9
O(6)-Cs-Cs#2	59.97(6)	O(3)-C(10)-O(4)	125.8(3)
O(1)-Cs-Cs#2	114.02(4)	O(3)-C(10)-C(9)	118.3(2)
O(7)-Cs-Cs#2	150.69(5)	O(4)-C(10)-C(9)	115.8(2)
C(14)#1-Cs-Cs#2	102.98(7)	O(3)-C(10)-Cs	47.86(15)
C(10)-Cs-Cs#2	149.13(4)	O(4)-C(10)-Cs	112.55(19)
Cs#1-Cs-Cs#2	122.373(7)	C(9)-C(10)-Cs	110.20(16)
Cs#3-Cs-Cs#2	112.969(9)	O(5)-C(11)-C(13)	110.5(2)
O(3)#1-Cs-H(6B)	104.5(10)	O(5)-C(11)-C(9)	106.1(2)
O(7)#2-Cs-H(6B)	86.1(11)	C(13)-C(11)-C(9)	110.6(2)
O(3)-Cs-H(6B)	102.4(11)	O(5)-C(11)-H(11)	109.9
O(6)-Cs-H(6B)	14.4(11)	C(13)-C(11)-H(11)	109.9
O(1)-Cs-H(6B)	77.9(10)	C(9)-C(11)-H(11)	109.9
O(7)-Cs-H(6B)	48.4(10)	O(5)-C(12)-H(12A)	109.5
C(14)#1-Cs-H(6B)	151.4(10)	O(5)-C(12)-H(12B)	109.5
C(10)-Cs-H(6B)	99.7(11)	H(12A)-C(12)-H(12B)	109.5

Cs#1-Cs-H(6B)	108.8(11)	O(5)-C(12)-H(12C)	109.5
Cs#3-Cs-H(6B)	123.2(11)	H(12A)-C(12)-H(12C)	109.5
Cs#2-Cs-H(6B)	49.5(10)	H(12B)-C(12)-H(12C)	109.5
O(3)#1-Cs-H(7B)	104.9(9)	C(14)-C(13)-C(11)	124.3(3)
O(7)#2-Cs-H(7B)	116.2(6)	C(14)-C(13)-H(13)	117.9
O(3)-Cs-H(7B)	49.0(5)	C(11)-C(13)-H(13)	117.9
O(6)-Cs-H(7B)	131.0(4)	C(13)-C(14)-Cs#1	110.4(2)
O(1)-Cs-H(7B)	62.5(8)	C(13)-C(14)-H(14A)	120.0
O(7)-Cs-H(7B)	13.9(4)	Cs#1-C(14)-H(14A)	75.8
C(14)#1-Cs-H(7B)	70.9(6)	C(13)-C(14)-H(14B)	120.0
C(10)-Cs-H(7B)	42.7(4)	Cs#1-C(14)-H(14B)	84.0
Cs#1-Cs-H(7B)	73.2(9)	H(14A)-C(14)-H(14B)	120.0
Cs#3-Cs-H(7B)	49.7(8)		

Symmetry transformations used to generate equivalent atoms

Table 6:Anisotropic displacement parameters (A^2 x 10^3) for 292. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U12]

Atom	U11	U22	U33	U23	U13	U12
Cs	43(1)	36(1)	34(1)	-1(1)	-5(1)	2(1)
N	24(1)	21(1)	20(1)	-1(1)	3(1)	-1(1)
O(1)	33(1)	28(1)	24(1)	0(1)	-2(1)	1(1)
O(2)	28(1)	28(1)	31(1)	5(1)	3(1)	1(1)
O(3)	34(1)	39(1)	25(1)	-1(1)	3(1)	-7(1)
O(4)	31(1)	38(1)	31(1)	-6(1)	13(1)	-8(1)
O(5)	25(1)	47(1)	22(1)	-1(1)	8(1)	-3(1)
O(6)	38(2)	41(2)	88(2)	-22(2)	11(2)	-6(1)
O(7)	83(2)	34(1)	35(1)	6(1)	22(1)	15(1)
C(1)	23(1)	26(1)	21(1)	-1(1)	6(1)	-1(1)
C(2)	19(1)	27(1)	21(1)	-1(1)	5(1)	-2(1)
C(3)	27(1)	26(1)	26(1)	-1(1)	7(1)	-2(1)
C(4)	26(1)	29(2)	32(2)	-7(1)	8(1)	-5(1)
C(5)	24(1)	41(2)	23(1)	-7(1)	4(1)	-5(1)
C(6)	22(1)	37(2)	23(1)	1(1)	3(1)	-1(1)
C(7)	20(1)	29(1)	21(1)	0(1)	6(1)	-2(1)
C(8)	20(1)	29(2)	22(1)	2(1)	6(1)	-1(1)
C(9)	22(1)	22(1)	23(1)	-1(1)	2(1)	-2(1)
C(10)	29(1)	20(1)	26(1)	-2(1)	7(1)	-2(1)
C(11)	22(1)	26(1)	22(1)	0(1)	4(1)	-2(1)
C(12)	29(2)	48(2)	33(2)	-1(1)	13(1)	-3(1)
C(13)	32(2)	27(2)	38(2)	-1(1)	12(1)	-4(1)
C(14)	50(2)	46(2)	36(2)	1(2)	6(2)	-23(2)

Table 7: Hydrogen coordinates (× 10^4) and isotropic displacement parameters (A^2 × 10^3) for 292.

Atom	x	y	z	U(eq)
H(6A)	2010(90)	820(50)	1670(40)	80(20)
H(6B)	2610(70)	1770(50)	1830(40)	75(18)
H(7A)	9510(60)	940(40)	-390(20)	63(15)
H(7B)	9340(70)	830(30)	370(30)	74(17)
H(3)	9897	3407	3170	31
H(4)	11741	3889	4422	34
H(5)	12933	2694	5413	35
H(6)	12360	953	5170	33
H(9)	8842	-1137	2626	27
H(11)	5477	-108	2191	28
H(12A)	3647	-169	3191	53
H(12B)	4455	-447	4139	53
H(12C)	4005	-1327	3459	53
H(13)	6278	-2246	2396	38
H(14A)	3369	-1271	1441	53
H(14B)	3760	-2498	1481	53

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